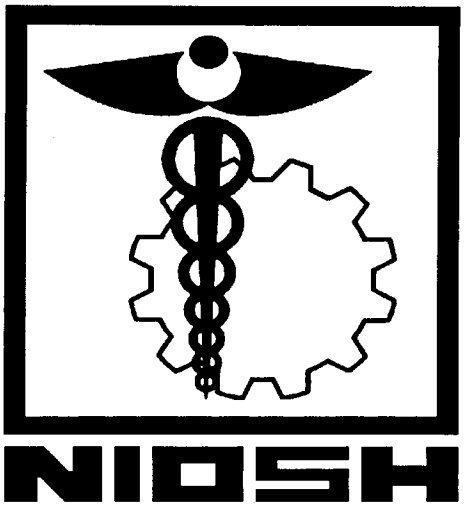
NIOSH

RESEARCH AND DEMONSTRATION GRANTS

FISCAL YEAR 1993



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

August 1994

DISCLAIMER

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DHHS(NIOSH) Publication No. 94-131

FOREWORD

The National Institute for Occupational Safety and Health (NIOSH) is mandated by the provisions of the Occupational Safety and Health Act of 1970 and the Federal Mine Safety and Health Amendments Act of 1977 to conduct research and demonstrations relating to occupational safety and health. Our overall goal is the prevention of illnesses, injuries, and deaths. Recognizing the valuable contributions of extramural scientists to this endeavor, NIOSH sponsors outstanding research through a grants program, which complements the Institute's intramural research program. The creativity and special resources available in the scientific community make the grants program a key component in achieving the Nation's goal to have safe jobs and healthy workers. We anticipate an expanded extramural research program in the coming years.

To maximize the grants program's usefulness in protecting workers, NIOSH funds projects that are scientifically sound and related to program priorities. We are interested in funding grants that will ultimately be of practical value in solving workplace problems.

This report provides a readily available source of information on the status and scope of the research grants program of NIOSH (all active grants during fiscal year 1993: October 1, 1992, to September 30, 1993). It is also intended to stimulate the submission of more proposals for high quality research on significant occupational safety and health concerns. We invite investigators in the biomedical sciences, engineering, and related disciplines to become partners in preventing United States workers from suffering adverse effects caused by occupational hazards.

Linda Rosenstock, M.D.
Director, National Institute for
Occupational Safety and Health
Centers for Disease Control and Prevention

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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 11,000 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?

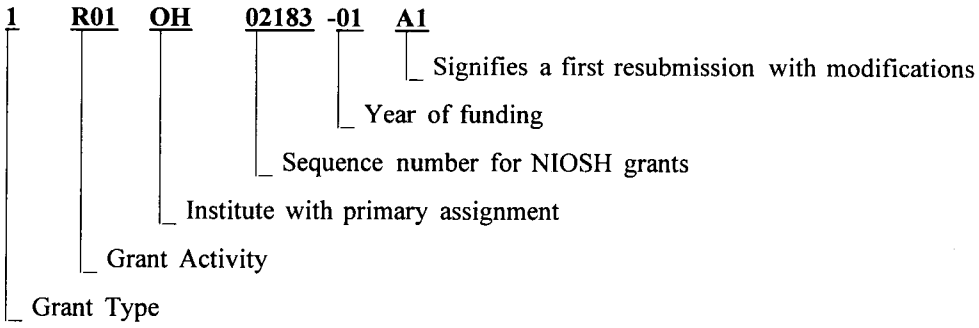
Contact NIOSH at the following address and telephone number:

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

The first component of an application number which identifies the type of application that has been submitted.

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

Grant Activity

This three-digit code indicates the activity to which application is being made.

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

This two letter code identifies the primary funding institution.

OH - NIOSH

Sequence Number

Five-digit serial numbers are assigned in sequence.

Year of Funding

This 2-digit number identifies the budget period of a project. An 01 indicates the first year of the grant award and the series of years continues through succeeding renewals.

Department of Health and Human Services
Centers for Disease Control and Prevention (CDC)
National Institute for Occupational Safety and Health

Research and Demonstration Grants
Occupational Safety and Health
PA-94-021

A. Introduction

The Centers for Disease Control and Prevention (CDC), National Institute for Occupational Safety and Health (NIOSH), is soliciting grant applications for research and demonstration projects relating to occupational safety and health, including the construction industry (see "FUNDS AVAILABLE").

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 domestic and foreign non-profit and for-profit organizations, universities, colleges, research institutions, and other public and private organizations, including State and local governments and small, minority and/or woman-owned businesses.

D. Availability of Funds

For fiscal year (FY) 1994, the budget for research grants is $9,250,000. Of that amount, about $5,500,000 is for non-competing continuation awards, and $3,750,000 is for new and competing renewal awards. Of the money for non-competing continuation awards, $1,200,000 is committed to provide ongoing support for construction grants that were started last year under a new initiative that was announced in a FY 1993 request for applications (OH-93-001). Of the money for new and competing renewal awards, $1,250,000 is for new construction grants, which is an expansion of the FY 1993 initiative. **Note that construction grant applications must be received by the March 1, 1994, deadline in order to be considered for funding with this new money.**

The projected breakdown for the $3,750,000 in new and competing renewal awards by type of grant mechanism is as follows: R01 and R18 grants - 19 awards for $3,000,000 (total costs of these currently awarded grants range from $50,000 to $350,000 with the average of about $170,000); K01 grants - 4 awards for $200,000 (total costs are limited to $54,000 per award); and R03 grants - 14 awards for $550,000 (total costs are about $37,500 per award).

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.

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity to reduce morbidity and mortality and improve the quality of life. This program announcement is related to the priority area "Occupational Safety and Health." Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0) or "Healthy People 2000" (Summary Report, Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-783-3238).

F. Purpose

The purpose of this grant program is to develop knowledge that can be used in preventing occupational diseases and injuries. NIOSH will support the following types of applied research projects: causal research to identify and investigate the relationships between hazardous working conditions and associated occupational diseases and injuries; methods research to develop more sensitive means of evaluating hazards at work sites, as well as methods for measuring early markers of adverse health effects and injuries; control research to develop new protective equipment, engineering control technology, and work practices to reduce the risks of occupational hazards; and demonstrations to evaluate the 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 funded for 12-month budget periods in project periods up to 5 years for research project grants and demonstration project grants; 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 the causes of work-related diseases and injuries.

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 of implementing a new/improved innovative procedure, method, technique, or system for preventing occupational safety or health problems. The project should be conducted in an actual workplace where a baseline measure of the occupational problem will be defined, the new/improved approach will be implemented, a follow-up measure of the problem will be documented, and an evaluation of the benefits will be conducted.

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 persons lawfully admitted to the U.S. for permanent residence (resident alien) 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 per year in direct costs for salary support (plus fringe benefits), technical assistance, equipment, supplies, consultant costs, domestic travel, publications, and other costs. 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 the proposed research project, 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).

4. Small Grants (R03)

The small grant program is intended to stimulate proposals from individuals who are considering a research career in occupational safety and health; as such, the minimum time commitment is 10%. It is expected that a recipient would subsequently compete for a career development grant (K01 - see section G.3.) or for a traditional research project grant (R01 - see section G.1.) related to occupational safety and health. The award is not intended to supplement ongoing or other proposed research; nor is it intended to be a mechanism for providing institutional support.

The small grant investigators must be U.S. citizens or persons lawfully admitted to the U.S. for permanent residence (resident alien) at the time of application who are predoctoral students, post-doctoral researchers (within 3 years following completion of doctoral degree or completion of residency or public health training), or junior faculty members (no higher than assistant professor). If university policy requires that a more senior person be listed as principal investigator, it should be clear in the application which person is the small grant investigator. Except for applicants who are assistant professors, there must be one or more named mentors to assist with the project. A biographical sketch is required for the small grant investigator, as well as for the supervisor and other key consultants, as appropriate.

This non-renewable award provides support for project periods of up to two years to carry out exploratory or pilot studies, to develop or test new techniques or methods, or to analyze data previously collected. Awards will not exceed $25,000 per year in direct costs for salary support (plus fringe benefits), technical assistance, equipment, supplies, consultant costs, domestic travel, publications, and other costs. The indirect

costs will be based upon the negotiated indirect cost rate of the applicant organization. An individual may not receive more than two small grant awards, and then, only if the awards are at different stages of development (e.g., doctoral student, post-doctoral researcher, or junior faculty member).

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 "Technical Information Contact, Dr. Roy M. Fleming, listed in this announcement under "**P. Where to Obtain Additional Information**."

The NIOSH Program Priorities are:

- Occupational lung diseases: related to agriculture, the mining industry, or exposure to fibers; occupational asthma; longitudinal pulmonary function assessment; eradication of silicosis.
- Musculoskeletal injuries: disorders of the back, trunk, upper extremities, neck, lower extremities; vibration white finger disease.
- Occupational cancers (other than lung): leukemia, mesothelioma, cancers of the bladder, nose, liver, and skin.
- Severe occupational traumatic injuries and fatalities: amputations, fractures, falls, eye loss, lacerations, and intentional and non-intentional fatal injuries.
- Cardiovascular disease: hypertension, coronary artery disease, acute myocardial infarction.
- Disorders of reproduction: congenital malformations, spontaneous abortion, and infertility.
- Neurotoxic disorders: peripheral neuropathy, toxic encephalitis, neuroses, extreme personality changes (exposure-related).
- Noise-induced hearing loss.
- Dermatologic conditions: dermatoses, burns (scalding), chemical burns, contusions (abrasions).
- Psychological disorders: affective disturbances such as anxiety, depression and job dissatisfaction; mal-adaptive behavior and lifestyle patterns; aggression; stress and post traumatic stress disorders; substance abuse.
- 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, safe work practices, personal protective equipment.
- Respirator Research: new and innovative respiratory protective devices including air-purifying respirators to protect against biological and/or infectious agents, developing active and passive end-of-service-life indicators, workplace protection and quantitative fit factors for powered air-purifying respirators, effectiveness of respiratory programs, physiologic and ergonomic factors, medical surveillance strategies, psychological and motivational aspects of respirator use, effectiveness of sorbents and filters (including chemical and physical properties),

I. Inclusion of Minorities and Women in Study Populations

Applicants are required to give added attention (where feasible and appropriate) to the inclusion of minorities and/or women study populations for research into the etiology of diseases, research in behavioral and social sciences, clinical studies of treatment and treatment outcomes, research on the dynamics of health care and its impact on disease, and appropriate interventions for disease prevention and health promotion. Exceptions would be studies of diseases which exclusively affect males or where involvement of pregnant women may expose the

fetus to undue risks. If minorities and/or women are not included in a given study, a clear rationale for their exclusion must be provided.

J. Applications Submission Deadlines and Review Dates

Applications are to be submitted on Form PHS-398 (revised 9/91). Forms should be available from the contacts listed under "**P. Where to Obtain Additional Information,**" or from:

Office of Grants Inquiries
Division of Research Grants, NIH
Westwood Building - Room 449
5333 Westbard Avenue
Bethesda, MD 20892

The original and five 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, MD 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	August 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	July 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.

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 mission of NIOSH.
     1) Relevance to occupational safety and health, by contributing to achievement of the research objectives specified in Section 20(a) of the Occupational Safety and Health Act of 1970 and Section 501 of the Federal Mine Safety and Health Amendments Act of 1977,
     2) Magnitude of the problem in terms of numbers of workers affected,
     3) Severity of the disease or injury in the worker population,
     4) Potential contribution to applied technical knowledge in the identification, evaluation, and/or control of occupational safety and health hazards, and
     5) Program balance, and
     6) Policy and budgetary considerations.

Questions regarding the above criteria should be addressed to the Technical Information Contact listed under "**P. 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

The Catalog of Federal Domestic Assistance number is 93.262.

O. Public Health System Reporting Requirements:

This program is not subject to the Public Health System Reporting Requirements.

P. Where to Obtain Additional Information

When requesting information, please refer to "PA-94-021" program announcement.

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Influence of Particles on Occupational Lung Disease

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Program Area: *Occupational Lung Diseases*
Grant Number: *5 R01 OH02277-03*
Start & End Dates: *09/30/89 – 03/31/94*
Funding Level: *$0 ($479,651 Cum)*

Importance to Occupational Safety and Health

Epidemiological 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 macrophage (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 other factors in 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

Alveolar macrophages (AM) were isolated by tracheal lavage from male Syrian hamsters (100–150 g, 8–9 wks old) and resuspended in 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) (BSA). Viability and the numbers of cells were determined by trypan blue staining procedure. The purity of AM was determined using cellular differential staining (Diff–Quik stain set Sci. Product Inc.). About $1x10^6$ cells in 2.5 ml RPMI–1640 were plated dish. The unattached cells were removed and the AM were incubated with various chemical treatments. Viability analyses were carried out at 24 and 48 hr time points. The remainder of the medium was extracted with ethyl acetate. The ethyl acetate extract was analyzed by HPLC to quantify metabolites and parent compound. Additional studies were conducted to compare the extent of binding to DNA to the release of metabolites from the cell.

Significant Findings

Determination of the Physical Characteristics of Particles. All of the particles were of respirable size with a particle size distribution of greater than 98% less than 5 microns. The count median diameters for aluminum oxide and amorphous silicas were less than 0.36 microns while for crystalline silica the count median diameter was 0.83 microns and for ferric oxide it was 1.8 microns. The surface areas of the particles were consistent with the median diameters and the size distributions in that the values for the aluminum oxide and the amorphous silicas were large varying from 124.8 to 253.1 m^2/g. For crystalline silica and ferric oxide that had larger count median diameters, the surface areas were 4.3 and 10.8 m^2/g, respectively. Neither precipitated nor gelled silica contained any crystalline silica while fumed contained 1.6% crystalline silica. The results indicated that crystalline silica had a smaller surface area and a larger count median diameter than any of the amorphous silicas.

Determination of AM to Phagocytize Particles and the Cytotoxicity of Particles to AM. Comparative viability studies of the AM in the presence of ferric oxide, aluminum oxide, or silica (crystalline, and gelled, fumed, and precipitated) were undertaken to determine noncytotoxic doses during phagocytosis. Doses of particles ranged from 0.0 to 0.5 mg. The viability of the hamster AM in the presence of aluminum oxide and ferric oxide up to the highest dose was similar to controls. After 24 and 48 hours, the viability of the AM for aluminum oxide and ferric oxide was approximately 80 and 70%, respectively. In the presence of silica, the viability of the hamster AM was similar to controls up to 0.01 mg and at least 80 and 66% at 24 and 48 hours respectively with the exception of precipitated silica at 48 hours where the viability was 57%. At doses

of 0.05 mg and 0.1 mg of crystalline, precipitated or fumed silica, at 24 hours the viability dropped to 70 and 45%, respectively, and at 0.5 mg the viability dropped to zero. With gelled silica the viability of the AM decreased to 27% at 0.05 mg and zero at 0.1 mg at 24 hours. These data are consistent with the physical characteristics in that the particle with the largest surface area is the most cytotoxic i.e. gelled silica followed by the other forms of silica. The data indicate that the count median diameter of less than .38 microns is sufficient for AM silica cytotoxicity. It would appear that the dose, surface properties and particle size are all important in the cytotoxicity of AM to silica.

Determination of Metabolic profiles from BaP–coated Particles. The data indicate that the major pathway is through the dihydrodiol formation. The 7,8–diol metabolite which is the precursor of the ultimate metabolite 7,8–diol–9,10–epoxide is higher in all of the particle associated BaP relative to BaP alone. This would suggest that BaP–coated particle is metabolized more readily through the active pathway than by BaP itself which would suggest a change in the metabolic pattern due to particle. Of the particles studied the values for the 7,8–diol were higher for the amorphous silicas than that of Fe_2O_3 or crystalline silica.

The level of DNA–binding from BaP–coated particles. The BaP–coated particles were incubated with AM and after 24 hours the AM were isolated. The DNA was isolated using a phenol extraction method and analyzed by ^{32}P–postlabeling techniques. The data indicate that both qualitatively and quantitatively that the BaP–adduct patterns have been altered by the presence of particles. In all cases, ppt, crystalline or Fe_2O_3 adduct #2 is the predominant adduct as opposed to the presence of all three adducts for BaP alone. These data are consistent with the metabolism data previously reported in that particles appear to alter both the metabolic pattern in the media and adduct pattern in AM. What is evident is that particle with the larger surface areas appears to have an increased alteration of the formation of BaP produced active metabolite intermediates.

In summary, BaP–coated particles in comparison with BaP alone have an impact on the metabolism, DNA binding and the extent of adduction. Additionally, dose as well as surface area and surface characteristics of particles are important determinants in the metabolism, DNA binding and cytotoxicity parameters of particles and BaP–coated particles.

Publications

Warshawsky D, Reilman R, Cheu J, Radike M, Rice C: Influence of Dose, Particle Size and Surface Area of Crystalline and Amorphous Silica on the Cytotoxicity to Hamster and Rat Pulmonary Alveolar Macrophage. J Toxicol Environ Health 38:399–417, 1993

Griefe A, Warshawsky D: Influence of Dose, Particle Size and Surface Area of Crystalline and Amorphus Silica on the Cytotoxicity to Hamster and Rat Pulmonary Alveolar Macrophage. J Toxicol Environ Health, accepted, 1993

Lung Disease in Chinese Textile Workers

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Program Area: *Occupational Lung Diseases*
Grant Number: *5 R01 OH02421-04*
Start & End Dates: *07/01/91 – 06/30/95*
Funding Level: *$139,344 ($423,931 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 11–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 11-year follow-up with surveys done at years 0, 5, and 11. Respiratory questionnaire, pulmonary function, and air sampling were performed at both surveys using identical techniques. Retirees and workers on leave were contacted and tested at years 5 and 11. The cause of death, as well as other reasons for loss from cohort, has been ascertained on all subjects.

Significant Findings

Significant findings of the 5-year follow-up study include: (1) a generally good dust-endotoxin correlation in the mill environments; (2) workers with both non-specific and work-related symptoms at the time of first survey had accelerated 5-year losses in lung function; (3) after appropriate adjustments for smoking, age, etc., cotton textile workers had an accelerated loss of FEV_1 over 5 years; (4) cotton-exposed workers, but not silk workers, with a greater than or equal to across-shift loss in FEV_1 at the time of first survey had significantly greater 5-year loss in FEV_1 after appropriate adjustments.

Data collection for the 11-year follow-up was completed by July, 1993. Ninety percent follow-up is expected. Data analysis on the 11-year follow-up has begun.

Publications

Christiani DC, Wegman DH, Ye TT, Eisen EA: Variability in Symptom Reporting, Across-shift Drop in FEV_1, and Longitudinal Change in Pulmonary Function in Cotton Textile Workers. Chest, in press, 1994

Hayes G, Ye TT, Lu PL, Dai HL, Christiani DC: Respiratory Disease in Chinese Textile Workers, III: Assessment of Small Airways Function. Environmental Research, in press, 1994

Beckett WS, Pope CA, Xu XP, Christiani DC: Women's Respiratory Health in the Cotton Textile Industry: An Analysis of Respiratory Symptoms. Br Jour Ind Med 51:14-19, 1994

Christiani DC, Velazquez AV, Wilcox M, Olenchock SA: Airborne Endotoxin Concentrations in Various Work Areas within A Cotton Mill in Central America. Environmental Research, in press, 1993

Christiani DC, Wegman DH, Ye TT, Eisen EA, Olenchock SA: Cotton Dust - Gram Negative Bacterial Endotoxin Correlations in Two Mills. Am Jour Industr Med 23:333-343, 1993

Christiani DC: Occupational Diseases in the Industrializing and Industrialized World: Commonalities and Contrasts. Measurement Tools. Tubercle and Lung Disease 73:7-13, 1992

Velazquez AV, Christiani DC, McConnell R, Eisen EA, Wilcox M: Respiratory Disease in A Textile Factory in Nicaragua. Am Jour Industr Med 20:195-208, 1991

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 & Environmental Sciences 3:443-51, 1990

Christiani DC, Wegman DH, Ye TT, Eisen EA, Lu PL: A Longitudinal Study of Pulmonary Function in Chinese Cotton Textile Workers. American Review of Respiratory Diseases A589, 1990

Christiani DC, Wegman DH, Eisen EA, Ye Tt, Lu PL: Cotton Dust Exposure and Longitudinal Change in Lung Function. American Review of Respiratory Diseases 141:589, 1990

Airway Hyperresponsiveness Due to Cotton Dust

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Program Area: *Occupational Lung Diseases*
Grant Number: *5 R01 OH02593-04*
Start & End Dates: *09/01/89 – 08/31/95*
Funding Level: *$147,561 ($556,714 Cum)*

Importance to Occupational Safety and Health

Byssinosis remains a significant occupational health priority in the United States. Many textile workers exposed to cotton dust 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 hyperresponsivenss, a condition associated with the development of chronic airflow obstruction. By exploring the effects of cotton bract (a major component of cotton dust) extract (CBE) 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 (CBE) and will extend our previous observations concerning the interaction of cigarette smoking and other risk factors with byssinosis.

Objectives

Our specific aims are:

1. To investigate if cotton bract extract induces greater airway hyperresponsiveness in healthy smokers than in healthy non–smokers. The working hypothesis is that smokers have an asymptomatic, low–level airway inflammation that makes them more susceptible to in CBE–induced airway hyperresponsiveness.
2. Examine the effect of repeated CBE exposures on non–specific bronchial hyperresponsiveness. The working hypothesis is that repeated exposures to CBE result in progressively greater inflammatory changes in the airway that will manifest themselves by airway hyperresponsiveness.
3. To compare the bronchoconstrictor effect of CBE with a similarly prepared extract of cotton dust. The hypothesis is that the bronchoconstrictor agent(s) in cotton bract extract are the same or similar to those found in cotton dust and hence will provoke similar effects.
4. To examine the effect of asymptomatic airway hyperresponsiveness on the airway response to methacholine following CBE. The hypothesis is that non–specific mild airway hyperresponsiveness, which is widely distributed in the healthy population, contributes to airway hyperresponsiveness to CBE.
5. To examine the effect of atopic status on airway responsiveness following CBE. The hypothesis is that atopic status, in otherwise healthy individuals without airway symptoms may enhance CBE–induced airway hyperresponsiveness.

Methodology

Our laboratory has developed a clinical model for studying the effects of cotton dust on human airways. The model consists of measuring lung function changes resulting from aerosol challenge with CBE. Aerosol inhalation of CBE consists of a 10 minute challenge using tidal breathing for a total of 120 inhalations. Lung function is measured following these exposures using maximal and partial expiratory flow volume (MEFV and PEFV) curves. The main parameter of interest is the MEF40%(P) (the flow rate on the PEFV curve measured at 60% of baseline vital capacity below TLC).

In study 1 twenty–eight healthy non–smokers and fifty smokers were examined on two separate days. On the first day baseline airway reactivity to methacholine was established. On Day 2 the subjects first inhaled CBE following which lung function was measured for ninety minutes (at 15 minute intervals) and responsiveness to methacholine (PD20MEF40%(P)) was then determined. In study 2, 27 healthy non–smokers were examined on 7 separate days. On the first day we measured airway reactivity to methacholine (MC). On five consecutive days following the screening the subjects were challenged with CBE and again after 2 days on the eighth day. MC reactivity was determined 90 minutes after CBE challenge on days 1, 5 and 8. Study 3 compares airway responses to CBE and cotton dust extract (CDE) in 20 healthy subjects.

Studies 4 and 5 using a protocol similar to study 2 compares healthy subjects to subjects with atopy and with mild airway hyperresponsiveness.

Significant Findings

Studies 1 and 2 of this proposal have been completed and reported upon in full detail in the final report to NIOSH dated November 1992. The major significant findings of those studies were: CBE challenge caused significant drops (responders) in lung function (MEF40%(P) $\geq$ 20%) in 9/28 non–smokers and 27/50 smokers. Significant decreases in PD20MEF40%(P) were demonstrated for methacholine in smokers ($p \leq 0.01$) but not in non–smokers. When only responders were studied, MC responsiveness increased in non–smokers ($p \leq .001$) as well as smokers ($p \leq 0.005$). Repeated daily challenge with CBE in 27 non–smokers brought about accentuated lung function decline on day 1 and 8 but not on days 2 through 5.

We conclude that "naive" non–smoking subjects never exposed to cotton dust show characteristic bronchoconstrictor responses (Monday bronchoconstriction) when challenged daily with CBE. Airway hyperreactivity accompanies this response. Smoking is an independent cause for airway hyperreactivity and enhances the effect of CBE challenge.

Work is now well under way on studies 3,4 and 5. Data collection has been completed for study objective 3. Twenty subjects have been studied with CBE and CDE (obtained from NIOSH). In a preliminary analysis of 11 subjects there were 8 responders (R) to CBE and 9 (R) to CDE. All CBE responders were CDE responders. The average maximal response to CBE was a fall in MEF40%(P) to 68 $\pm$ 9/1% of baseline compared to 68 $\pm$ 6.8% for CDE (NS). All subjects R and non–responders (NR) enhanced their MC response following CBE and CDE. We conclude that both CBE and CDE exert similar physiologic effects in naive healthy adults.

In studies 4 and 5 which investigate the role of pre–existing airway hyper– responsiveness and pre–existing atopy on the response to CBE we have completed data collection on 38 subjects. Analysis of this preliminary data is not yet available.

Publications

Schachter EN, Zuskin E, Rienzi N, Godbold J: In Vitro Pharmacologic Studies of Poultry Dust Extract. Proceedings of the 18th Cotton Dust Conference, San Diego, in press, 1994

Schachter EN, Zuskin E, Buck M, Rienzi N, Godbold J, Castranova V, Whitner M, Siegel P: Comparison of the Airway Response To Cotton Dust And Cotton Bract Extracts. Proceedings of the 18th Cotton Dust Conference, San Diego, in press, 1994

Zuskin E, Mustajbegovic J, Schachter EN: Follow–up Study of Respiratory Function in Hemp Workers. Am J Ind Med, in press, 1994

Zuskin E, Mustajbegovic J, Schachter EN, Rienzi N: Respiratory Symptoms and Ventilatory Capacity in Workers in a Vegetable Pickling and Mustard Production Facility. Int Arch of Occupational and Environ Health, in press, 1993

Zuskin E, Schachter EN, Kanceljak B, Witek TJ, Jr., Fein E: Organic Dust Disease of Airways. Int Arch Occup Env Health 65:135–140, 1993

Schachter EN, Russomanno J, Siegal J, Fine E, Rienzi N, Witek TJ, Jr., Buck MG, Godbold J: Does Cotton Bract Extract Challenge Cause "Monday" Bronchospasm? Proc 17th Cotton Dust Conference, pp. 279–280, 1993

Castranova V, Robinson VA, Borger MW, Siegel PD, Judy JD, Schachter EN, Frazer DG: Pulmonary Response of Guinea Pigs To Inhalation of Purified Cotton Bract Extract. Proc 17th Cotton Dust Conference, pp. 248–251, 1993

Schachter EN, Tai A, Cardozo C, Zuskin E, Godbold J, Rienze N, Kesser M: Characterization of the Potentiation of Bradykinin–Induced Constriction By An Inhibitor of Endopeptidase 24.15. Am Rev Resp Dis 147:A851, 1993

Fein E, Godbold J, Chusid E, Schachter EN: The Effect of High Dose Steroids or Sleep Patterns and Respiratory Function in Symptomatic Steroid Dependent Asthmatics. Amer Rev Resp Dis, 147:A291, 1993

Zuskin E, Mustajbegovic J, Schachter EN: Respiratory Function in Sewage Workers. Am J Indust Med 23:751–763, 1993

Zuskin E, Butkovic D, Schachter EN, Mustajbegovic J: Respiratory Function in Workers Employed in the Glass Blowing Industry. Am J Indust Med 23:835–844, 1993

Zuskin E, Schachter EN, Mustajbegovic J: Respiratory Function in Greenhouse Workers. Int Arch of Occup and Environ Health 64:521–526, 1993

Schachter EN: Byssinosis. In: Textbook of Clinical, Occupational and Environmental Medicine, WB Saunders, Philadelphia, PA, in press, 1993

Zuskin E, Kanceljak B, Schachter EN, Witek TJ, Maayani S, Goswami S, Marom Z, Rienzi N: Immunological Findings in Hemp Workers. Env Res 59:350–361, 1992

Zuskin E, Kanceljak B, Mustajbegovic J, Schachter EN: Immunological and Respiratory Status in Swine Workers. Allergy 12:251, 1992

Zuskin E, Kanceljak B, Schachter EN, Witek TJ, Maayani S, Goswami S, Marom Z, Rienzi N: Immunological and Respiratory Changes in Animal Food Processing Workers. Am J Ind Med 21:177–191, 1992

Zuskin E, Zagar Z, Schachter EN, Ivankovic D: Respiratory Symptoms and Ventilatory Capacity in Swine Confinement Workers. Br J Ind Med 49:435–440, 1992

Schachter EN, Zuskin E, Mustajbegovic J, Buck MG, Maayani S, Marom Z, Goswami SK, Rienzi N: Pharmacologic Studies of Wool Dust Extract in Isolated Guinea Pig Trachea. Proc XVI Cotton Dust Research Conference, (Volume 1), pp. 290–291, 1992

Zuskin E, Ranceljak B, Schachter EN, Witek TJ, Mustajbegovic J, Maayani S, Buck M, Rienzi N: Immunological Findings and Respiratory Function in Cotton Textile Workers. Int Arch Occup Env Health 64:31–37, 1992

Schachter EN, Marom Z, Goswami S, Gollub E, Rienzi N, Maayani S: Purified Macrophage Mucus Secretagogue is A Potent Bronchial Smooth Muscle Relaxing Agent *In Vitro*. Am Rev Resp Dis 145:A374, 1992 (Abstract)

Cabrera M, Rienzi N, Schachter EN: Patterns of Asthma Admissions to A Metropolitan Hospital. 1990. Am Rev Resp Dis 145:A506, 1992

Zuskin E, Kanceljak B, Stilinovic L, Schachter EN, Kopjar B: Immunological Status and Respiratory Findings in Furriers. Am J Industr Med 21:433–442, 1991

Zuskin E, Ivankovic D, Schachter EN, Witek TJ: A Ten Year Follow–up Study of Cotton Textiles Workers. Amer Rev Resp Dis 143:301–305, 1991

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 XV, pp 214, 1991

Zuskin E, Kanceljak B, Witek TJ, Schachter EN: Acute Ventilatory Response to Green Coffee Dust Extract. Ann Allergy 66:219–224, 1991

Zuskin E, Kanceljak B, Schachter EN, Witek TJ, Marom Z, Goswami S, Maayani S: Immunological and Respiratory Changes in Soybean Workers. Int Arch of Occup Env Health 63:15–20, 1991

Zuskin E, Kanceljak B, Schachter EN, Mustajbegovic J, Goswami S, Maayani S, Marom Z, Rienzi N: Immunological and Respiratory Findings in Swine Farmers. Env Res 56:120–130, 1991

Russomanno J, Siegel J, Fine E, Rienzi N, Witek TJ, Buck MG, Godbold J, Schachter EN: Does Cotton Bract Extract Challenge Cause "Monday" Bronchospasm? Amer Rev Resp Dis 143:A428, 1991 (Abstract)

Russomanno J, Siegel J, Fine E, Rienzi N, Witek TJ, Buck MG, Godbold J, Schachter EN: The Interaction of Cotton Bract Extract and Methacholine in Smokers and Non–smokers. Amer Rev Resp Dis 143:A428, 1991 (Abstract)

Schachter EN, Marom Z: Erythromycin Reduces Airway Responsiveness to Methacholine. Amer Rev Resp Dis 143:A428, 1991

Schachter EN, Zuskin E, Cardoza C, Godbold J, Rienzi N, Lesser M: Inhibitor of Endopeptidase 24.15 Potentiates Bradykinin–induced Contraction of Guinea Pig Trachea. Amer Rev Resp Div 143:A616, 1991 (Abstract)

Goswami S, Gollub E, Slavin S, Schachter EN: Erythromycin Reduces Muscus Glycoprotein Secretion and Symptoms in Stable Chronic Bronchitis. Amer Rev Resp Dis 143:A669, 1991 (Abstract)

Fein E, Zuskin E, Rienzi N, Schachter EN: Prevalence of Chronic Respiratory Symptoms in Workers Exposed to Elevated Ambient Dust Levels. Fourth International Conference on Environmental Lung Disease, Montreal, p. 8, September 28, 1991

Schachter EN: Occupational Airway Disease. Mount Sinai J Med 58(6):483–493, 1991

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

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

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

Witek TJ, Mazzara CA, Zuskin E, Beck GJ, Buck MG, Schachter EN: Bronchial Responsiveness After Inhalation of Cotton Bract Extract. Am Rev Resp Dis 183:1579–83, 1988

Coal Dust Particle Size and Respiratory Disease

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Program Area: *Occupational Lung Diseases*
Grant Number: *5 R01 OH02761-02*
Start & End Dates: *09/01/90 – 08/31/93*
Funding Level: *$0 ($229,614 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 in primarily in the terminal airways and alveoli, as the basis of their exposure assessment. There are, however, good reasons to hypothesize that chronic bronchitis may be more specifically associated with exposure to larger particles of dust which deposit in the tracheo–bronchial tree. This study is designed to examine the independent effects of respirable and tracheo–bronchial dust fractions in the development of obstructive lung disease. In addition, most quantitative exposure–response studies rely upon simple cumulative exposure as the primary dose metric. This study will utilize the time period–specific quantitative exposure estimates to examine the assumptions inherent in simple cumulative exposure and to define a more appropriate metric for exposure response analyses.

Objectives

1. Characterize the particle–size distribution of dusts in underground coal mining operations based on personal exposure data.
2. Develop estimates of cumulative respirable and tracheobronchial dust exposures for a cohort of previously studied underground miners.
3. Explore the exposure–response functions for these exposure measures and the development of airflow limitations and symptoms of chronic bronchitis.
4. Explore the construction of simple cumulative exposure to identify an optimal exposure metric for the study of coal dust and obstructive lung disease.

Methodology

Particle–size distributions of dust exposure were characterized for a set of occupations identified from the work histories of miners participating in the National Study of Coal Workers' Pneumoconiosis. Four mines were visited and exposure to miners employed in the targeted occupations were monitored using a personal cascade impactor. Using a deposition model for pulmonary aerosols, the respirable and tracheo–bronchial dust fractions were calculated for each sample. The parameters were then compare across occupations, proximity to the coal face and by mining technology. Analysis of variance was used to consider the possible effects of these factors while simultaneously considering differences between mines. The potential for using these ratios of tracheo–bronchial to respirable dust fractions in conjunction with previously developed estimates of respirable dust concentrations to estimate respirable and tracheo–bronchial dust cumulative doses would then be explored. Exposure response functions using the alternative dose metrics could then be compared.

An alternative method for summarizing exposures over time was also developed that accounts for non–linear effects of exposure concentrations and time since exposure.

Significant Findings

Collection of particle size distribution data was accomplished at four underground Appalachian mines. The data included 180 valid samples obtained with the assistance of volunteer miners at each site using an 8–stage personal cascade impactor.

Findings from this effort indicated little variability between occupations, or groups of

occupations in the particle size distributions, or the ratio of respirable to tracheo–bronchial dust fractions. There was some difference observed between mines, which may have resulted from the use of diesel transportation equipment in one mine. The findings are somewhat at deviance to observations of previous researchers, however all previous data were obtained by area samples placed in positions which may have accentuated the different distributions.

The findings of this proposal made application of particle size–specific fractions to historical data infeasible so the original intent of estimating exposure–response relations using cumulative tracheo–bronchial dust exposures was not possible. However, the results also suggest that data collected as respirable exposure fractions should be equally predictive of obstructive disease, at least for historical reconstruction purposes.

Additional analysis of the relationship between respirable dust exposures and obstructive disease, especially symptoms of bronchitis and pulmonary function variables, was conducted prospectively on the previously analyzed cohort of 977 underground miners attending Round 2 and Round 4 of the National Study of Coal Workers' Pneumoconiosis (NSCWP). These findings suggest a steep exposure–response relationship between dust exposure and the incidence of bronchitis symptoms within a few years of onset of exposure. Further, the data suggest a strong relationship between bronchitis symptoms and loss of pulmonary function.

A further exploration of the dimensions of cumulative exposure resulted in a proposal to integrate time of exposure, dust concentration and exposure duration into a single flexible dose metric. The proposed metric uses exponents of the concentration and time of exposure components to estimate the optimal contribution of these factors in the development of disease. The metric was tested in the previously described cohort from the NSCWP, and the result suggested that the square root of concentration and the first power of time since exposure might be an optimal expression for cumulative exposure for low level coal dust exposure and decrements in forced expiratory volume in one second. For the incidence of wheezing, concentration and time since exposure squared may represent an improvement in a dose metric over simple cumulative exposure. The model is seen as experimental and application of this or similar models to other data sets will ultimately prove its utility.

Publications

Seixas NS, Robins TG, Becker M: A Novel Approach to the Characterization of Cumulative Exposure for the Study of Chronic Occupational Disease. Am J Epid 137:463–471, 1993

Seixas NS, Robins TG, Becker M: Determination of an Optimal Exposure Metric for the Study of Coal Dust Exposures and Obstructive Lung Disease. Am J Epid, in press, 1992

Detecting Lung Overload by Magnetometry

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Importance to Occupational Safety and Health

The concept of lung overload is based on observations made in chronic inhalation exposures of rats to high concentrations of coal dust, iron oxide, titanium dioxide, diesel engine exhaust and polymer particles. The accepted indicator of lung overload is a significant decrease in the alveolar clearance rate of particles. Besides decreased alveolar clearance, lung overload is associated with inflammatory responses in the alveoli (influx of neutrophilic leukocytes, protein leakage), macrophage accumulation, fibrotic changes and even tumors. Extrapolation of data from rats suggests that decreased particle clearance may occur in humans at a mass burden of 1–3 mg/g lung when inhaling particles of density 1 g/cm^3 and clearance could cease at 30 mg/g lung. Under reasonable assumptions for the deposition rate and clearance half–times in humans, the accumulated dust burden would exceed 3 mg/g lung after 1 1/2 years of exposure to "nuisance" dusts at the concentration of 5 mg/m^3, which is the present OSHA standard of exposure limit for respirable dusts. If pulmonary mass load in the range of 1–3 mg/g lung causes a decrement in clearance in humans, as it does in rats, then lung overload related effects might occur in humans inhaling concentrations of dust allowed by governmental regulations.

Magnetometry is the non–invasive measurement of the amount of ferro– and ferri–magnetic materials in a sample. If this technique could be adapted for use in humans to assess particle retention and

clearance, it would mean a great advancement to clarify questions regarding overload in humans.

Objectives

The long–term objectives of the proposed line of research are to characterize and clarify lung overload in rodents and to develop magnetometry to a level which makes assessment of overload in humans realistic. The overall aims of this project are to: (1) develop needed aerosol generation and magnetometry systems; (2) demonstrate that dust clearance rates can be measured reliably using magnetic aerosols, (3) test hypotheses which suggest that magnetometry may have unique capabilities to detect and characterize lung overload, and (4) compare results from two animal species to provide a broader information base for extrapolating to humans and for planning future human studies.

Methodology

The thorax of animals was placed in a strong DC magnetic field for a short time to align the magnetic moments of individual particles by both rotating particles and rotating magnetic domains within particles. After the magnetizing field was removed, the remanent field was measured by an array of 8 fluxgate magnetometers arranged such that the magnetic moment and subsequent relaxation of as little as 0.1 mg of magnetite in the lungs of rats could be recorded. In addition to the 8 magnetometers, the system consists of shielding, analog signal processing hardware and a computerized digital signal processing system. Rats were exposed nose–only to magnetite or to a mixture of magnetite and TiO_2 particles. When sacrificed the pulmonary tissue was analyzed chemically for iron and titanium in addition to a number of biological parameters (determined from lavage, e.g., cells, proteins).

Significant Findings

Using multiple exposures, magnetometric results clearly show the increase in lung burden during exposure and also clearance of magnetite particles when the exposure was discontinued. However, post–exposure clearance of particles based on magnetometry measurements seemed to be unexpectedly fast (up to T 1/2 = ~20 days) compared to clearance based on chemical analysis of magnetite (T 1/2 = ~150 days). The results with respect to clearance were similar after single or after repeated exposures and between magnetite and TiO_2 particles determined chemically. The magnetic signal seemed to be affected by some post–exposure processes. We tested the lung contents using x–ray crystallography and concluded that neither solubility nor changes of magnetite into a different form (e.g. hematite) can explain the discrepancy. Results of other experiments indicate that rearrangement of particle agglomeration affects magnetometric measurements. It is conceivable that during particle translocation within the lung such rearrangement may occur. Presently, we are performing studies on particle agglomeration and its effects on magnetometry in the post–exposure phase. We believe that a clarification of the discrepancy between the magnetometric and chemical clearance determination may be decisive for the practicality of using magnetometry in human studies.

In another experiments, rats were irradiated (thorax only) before particle exposure. The compromised AM may change the pulmonary tissue response at the time of exposure to magnetite which may show in the magnetometric results.

Publications

Ferin J, Oberdörster G, Soderholm SC: Magnetometric Analysis of Pulmonary Retention of Particles. Ninth Congress of the International Society for Aerosols in Medicine, J Aerosol Medicine 6, Supplement, pp 50, March 1993

Ferin J, Soderholm S, Oberdörster G: Quantitative Analysis of Particle Translocation Within the Lung. Am Rev Respir Dis 145(4):A801, 1992 (International Conference Supplement)

On-Site Enumeration of Fungal Spores and Bacteria in Air

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Importance to Occupational Safety and Health

The sampling and analysis methodology is expected to yield a measure of exposure to viable and nonviable bioaerosols that have been implicated in the occurrence of many diseases of the lower airways (e.g., hypersensitivity pneumonitis, organic dust toxic syndrome, asthma, aspergillosis, and bronchitis) and

diseases of the upper airways (e.g., allergic rhinitis and sinusitis). The onset of acute HP symptoms have been observed upon repeated exposures to high concentrations of fungi and actinomycete spores, viable and nonviable. Allergy–related diseases are often associated with specific organisms; the developed method will yield information that will aid in the identification of fungal spores and bacteria. The method will, also, allow timely on–site analyses which will facilitate the correlation of currently observed symptoms with exposure conditions and the development and interpretation of comprehensive sampling strategies. Sampling sequentially with the sampling manifold will allow the development of time and spatial concentration profiles over extended time periods which will aid in locating sources of bioaerosols and in the correlation of environmental conditions or work activities that may induce or influence the release of bioaerosols to the indoor air environment. The filter catch can be used for the determination of other proposed indices of exposure to bioaerosols, including avian and animal serum proteins, proteases, antigens, and endotoxins. The determination of individual exposures, i.e., personal samples, will be possible by the use of individual filter holders.

Objectives

1. The overall objective of the proposed work is to develop an on–site screening method involving air sampling with membrane filter discs and subsequent analysis by brightfield and epifluorescent microscopy after supravitally staining collected spores and bacteria.
2. The primary goal of the first phase of study was the development of an analysis protocol that can be used in the field and that will yield results within minutes of the cessation of air sampling. The developed sample preparation procedure should permit determinations of viability. The analysis method was developed and evaluated.
3. In the second phase, an air sampling device was fabricated that provides sequential sampling with replicates. The evaluation of this device is underway. Test atmospheres of a nonbiological fluorescent aerosol and representative fungal spores and bacteria are being produced in the laboratory for the evaluation of the sampling device and for the evaluation of the total sampling and analysis procedure.
4. The final phase of the proposed work, which will be undertaken in the third year, will be the field evaluation of the developed technique.

Methodology

For the development and evaluation of the analysis method, aliquots of aqueous suspensions of fungal spores and bacteria were deposited on Irgalan black–stained, track–etched polycarbonate filters with a pore size of 0.2 or 0.4 μm (Poretics, Bedford, MA), and the liquid was removed by vacuum. The levels of the bioparticles in suspensions were determined using a Coulter ZM counter. The bioparticles were stained without fixation with ≤2 mM acridine orange in neutral buffered saline; a coverslip was added and sealed with wax or clear nail polish. The slides were viewed with a binocular Leitz® Laborlux D fluorescent microscope with BP filter 450–490 nm, barrier filter 515 nm, and 100x (1.25–0.60 Oel) oil immersion objective, and 12.5x eyepieces (Leica Mikroskopie und Systeme GmbH, D–6330, Wetzlar, Germany). For the ongoing evaluation of the sampling method, bioaerosols have been collected on 13–mm diameter filters in the designed sampling manifold and prepared for viewing as specified above.

The laboratory evaluation of the developed sampler is being carried out in a wind tunnel, which is a 10–ft (3.0–m) length of 22.8 in. (0.56 m) ID, 26.0 in. (0.66 m) OD PVC pipe coated on the inside with a graphite–containing paint that renders the pipe conductive to ground. A high efficiency particulate air (HEPA) filter is installed at each end of the pipe to purify the inlet air and to remove the generated aerosol before exhausting air from the system. A centrifugal fan powered by a 1.5 hp (1750 rpm) motor is used to pull air through the system so that the tunnel is under negative pressure when being used.

Significant Findings

Mean bacterial counts >100 yielded CVs ≤13% except for two out of 18 sets of replicates. Mean spore counts >100 yielded CVs ≤12%. The conclusion was drawn that, if biases were small, counts of individual particles and aggregates with accuracies ≤25% could be obtained as long as counts were greater than 100. The limit of quantitation (LOQ) was defined as 100 particle counts for which the CV was ≤13%. The limit of detection (LOD) was defined as a single particle count because blank polycarbonate filters were consistently found to be free of bacteria and fungal spores. Desiccation of osmotically fragile *E. coli* on filters exhibited no effects on morphology or the enumeration of the bacteria. Microscopic examination of fungal spores and of colonies grown as pure cultures demonstrated the utility of bright field and epifluorescent microscopy not only as useful tools in the enumeration of bioaerosols but also in the

identification of fungi. A sampling system was designed with variable cutpoints to offer the opportunity for sampling thoracic–sized aerosols and larger particles when desired. One of the primary design features is a sampling manifold to allow the collection of replicate samples over sequential sampling periods. Laboratory and field tests are currently being conducted with the sampler.

Metal Fume Fever

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Program Area: *Occupational Lung Diseases*
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Start & End Dates: *09/30/92 – 09/29/95*
Funding Level: *$218,211 ($477,442 Cum)*

Importance to Occupational Safety and Health

Metal fume fever is a common occupational illness caused by inhalation of freshly generated zinc oxide and other metal fumes. This illness is characterized by fever, systemic symptoms, and mild lung inflammation with onset several hours after the acute exposure. Repeated exposure results in adaptation with reduction in symptoms and febrile response. There is little information regarding dose–response relationships in naive and chronically exposed individuals, the nature of adaptation to the acute response, or the mechanism by which zinc oxide exposure causes metal fume fever.

Objectives

Our laboratory has developed a quantitative zinc oxide fume generating, monitoring, and exposure system for animal and human subjects. Using this system, we have previously demonstrated: (1) systemic effects in humans at the current OSHA PEL of 5 mg/m^3; (2) induction of human zinc–binding protein (metallothionein) after exposure; (3) acute lung inflammation in animals exposed below the PEL; and (4) alterations in cytokine release from guinea pig lung inflammatory cells. To further understand acute and adaptive responses to zinc oxide exposure and to determine the mechanism by which it causes metal fume fever, the following hypotheses will be tested: (1) acute, febrile, and pulmonary responses to exposure in human subjects occur at and below the current OSHA PEL; (2) adaptive responses to chronic exposures in humans do not eliminate lung inflammatory changes; (3) adaption involves changes in nasal epithelial metallothionein gene induction; (4) mechanism of metal fume fever and adaption involves release of cytokines and a modulation of their response at a central or peripheral level in zinc oxide–exposed animals.

Methodology

Using a carefully controlled quantitative pure zinc oxide fume generating system, naive subjects and workers chronically exposed to zinc oxide fume will be exposed for two hours at concentrations below the current OSHA PEL. Symptoms, fever, peripheral blood indices of inflammation and nasal epithelial induction of metallothionein will be assessed. The ability for these low levels of zinc oxide fume to induce inflammatory changes in the lung will be assessed by lavage of lung lining fluid. These studies will be accomplished using an integrated multi–disciplinary approach and should yield important insights into the genesis and adaption of this debilitating occupational illness.

Significant Findings

Using this exposure system, we have demonstrated our ability to expose human subjects to zinc oxide fume for two hours at and below the current OSHA TLV in a blinded fashion. Subjects have developed characteristic symptoms of metal fume fever as well as symptoms in proportion to their exposure level.

In related animal studies, we have found that mice which have previously received repeated daily exposure to zinc oxide fume at 5 mg/m^3 have greater inducibility of lung metallothionein gene expression to a single zinc oxide exposure than naive mice.

Additional human subjects are currently under study to test the hypotheses noted as objectives above.

Publications

Cosma GN, Chen LC, Currie D, Garte SJ, Gordon T: Metallothionein (MT) and Cytokine Gene Expression Following Single and Repeated Inhalation to Metal Fumes. The Toxicologist, in press, 1994 (Abstract)

Gordon T, Fine J: Metal Fume Fever, In: Occupational Medicine, State of the Art Reviews. De novo Toxicants: Combustion Toxicology, Mixing Incompatibilities, and Environment Activation of Toxic Agents, (eds. DJ Shusterman, JE Peterson),

Philadelphia, Hanley and Belfus, Vol 8, pp. 505–518, 1993

Pulmonary Effects of Machining Fluid Aerosols

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Program Area: *Occupational Lung Diseases*
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Start & End Dates: *09/01/93 – 08/31/95*
Funding Level: *$97,953 ($97,953 Cum)*

Importance to Occupational Safety and Health

This research proposal will examine the acute and subchronic pulmonary effects of machining fluid aerosols – an occupational hazard for nearly 1 million workers in this country. Machining fluids/cutting oils are hypoosmolar, alkaline fluids which are frequently contaminated with a variety of microbial agents.

Objectives

The major goals of the proposed studies are to (1) determine the roles of contaminating endotoxin, hypotonicity, and alkalinity in the adverse pulmonary effects associated with occupational exposure to machining fluid aerosols; and (2) compare the potential of different classes of machining fluids to produce inflammatory and functional changes in the lung. The proposed studies will determine in an animal model whether subclinical inflammatory changes may persist in the lung after repeated exposure to machining fluid aerosols at exposure concentrations near the current TLV. The proposed experiments will help to provide a clearer understanding of the role of microbial contamination in the pulmonary effects of inhaled machining fluid aerosols.

Methodology

Adverse pulmonary effects after single and repeated exposures to machining fluid aerosols will be examined using functional, biochemical, and morphological techniques in a sensitive guinea pig model. Animals will be exposed to aerosols of water (the control atmosphere), used machining fluids, or unused machining fluids. During the single exposures, non–invasive measurements of airway resistance will be performed at hourly intervals. In the repeated exposure protocol, measurement of nonspecific airway responsiveness will be performed prior to initiation of, at 2 week intervals during, and at the end of exposure.

Significant Findings

None to date.

Occupational Disease Among Carpenters

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Start & End Dates: *09/30/93 – 09/29/95*
Funding Level: *$177,290 ($177,290 Cum)*

Importance to Occupational Safety and Health

The National Institute for Occupational Safety and Health (NIOSH) has identified occupational lung diseases as one of the ten leading occupational health problems in the United States. The construction industry has been identified as one of the "Special Population Targets" in the Health People 2000 document due to the high rate of work–related deaths and work related injuries among this population. Additionally, occupational respiratory disease surveillance data for 1973–1988, calculated from Bureau of Labor Statistics data, demonstrate annual incidence rates to range from 1.8 to 3.7 cases per 10,000 full–time workers for the construction industry.

Surveillance is the first step in development of prevention strategies for leading work–related diseases and injuries. Unfortunately, no single comprehensive data base is available to study occupational illness/disease/injury. With no surveillance mechanism in place, a number of avenues have been explored including the use of

pre–existing data bases such as state worker's compensation files and health insurance claims.

The use of data bases for epidemiologic research that were developed for other purposes raises a number of issues. Morbidity information relative to occupational injuries and illness can be collected from worker's compensation data and from health insurance claims. Collectively, use of both of these data sources is necessary to fully characterize occupational morbidity and the interaction of occupational and other risk factors. This project will explore the use of medical claims data for study of occupational lung disease among carpenters in Washington State.

Objectives

The major objective of this proposed research project is to study work–related respiratory disorders among members of the United Brotherhood of Carpenters (UBC) international union. Specific aims are as follows:

1. To integrate several existing databases in order to develop a comprehensive data system useful for study of work–related respiratory disorders among carpenters. These databases include: (a) medical claims data, (b) worker's compensation data, (c) UBC national membership file data, and (d) disability and pension data. This study will be conducted using data for Washington State.
2. To develop epidemiological methods for analyses of medical claims data. This includes development of appropriate case definitions for purposes of surveillance and etiologic epidemiology of respiratory diseases.
3. To analyze these integrated data with respect to incidence and prevalence of occupational lung diseases among carpenters in Washington State. These analyses will have the objective of identifying high risk industries and carpenter sub–trades.
4. To conducted an asthma case–control study of carpenters for purposes of identifying possible etiologic associations with specific occupational exposures.

Methodology

Occupational lung diseases to be studied include malignant neoplasms (ICD–9 158, 162, 163), obstructive pulmonary diseases (IDC–9 406–496) and pneumoconioses (ICD–9 500–508). Case definition criteria using ICD–9 codes will be used to identify existing and new cases of each target lung disorder using both worker's compensation data and insurance data. In order to calculate rates, estimates of the populations covered will be derived from computer tapes of all eligible members covered by the insurance Funds for the chosen study years. Analyses will include generation of conventional descriptive statistics as well as more refined internal comparisons. Age, race and sex specific incidence and period prevalence rates with confidence limits based on Poisson statistics will be calculated for each target lung disease. For identification of high risk populations, further analyses will include calculation of age–adjusted incidence and period prevalence rates for each lung disease for various carpenter trades and industries in Washington.

The proposed case definition of asthma for the case–control study will be a primary ICD–9 diagnosis code of 493. The case–control study will include newly diagnosed cases of asthma during 1988–1992 (estimated to be 100–150) from the medical claims file or the State of Washington Worker's compensation files. Three controls for each case, group matched on age (within 2 years), sex and race will be randomly selected from the population of carpenters who do not file a medical or compensation claim for lung diseases of interest during the study period.

Cases and controls will be contacted by mail and asked to complete a self–administered questionnaire soliciting information concerning respiratory symptoms as well as information concerning specific occupational exposures possibly associated with occupational asthma. The occupational/environmental exposure questionnaire will include questions concerning exposures to wood dusts, isocyanates, anhydrides, metals, soldering fluxes, paints, solvents plants, animal products and other biological and chemical materials. Stratified analyses will be used to control for possible confounders such as age, race, sex, smoking, etc. Multiple logistic regression will be used to analyze the association between asthma diagnosis, respiratory symptom data (and combinations of symptoms) and occupational exposures after adjustment for potential confounders.

Significant Findings

This research is just underway. Preliminary analyses of the medical claims data have shown the following number of persons filing claims for lung disorders of interest during 1988–92:

Malignant Neoplasms (ICD–9 158, 162, 163) – 149
Obstructive Pulmonary diseases (IDC–9 406–496) – 2796
Pneumoconioses (ICD–9 500–508) – 58

Effects of Zinc Oxide Welding Fume Inhalation

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Start & End Dates: *09/28/90 – 09/27/93*
Funding Level: *$0 ($157,960 Cum)*

Importance to Occupational Safety and Health

The self–limited systemic illness following zinc oxide fume inhalation consists of a flu–like illness: malaise, myalgia, and fever ranging from 38 to 39 degrees. The mechanisms underlying zinc induced MFF have not previously been clearly elucidated. However, animal and limited previous human data suggest that zinc oxide fume inhalation leads to a marked pulmonary inflammatory cellular response. The lung may be more than merely a route of exposure, but instead may play an important role initiating the metal fume fever response. Although the syndrome of metal fume fever has been studied experimentally since the early 1900's, explanations of its mechanism have remained speculative. The hypothesis of this study has been that the effects of zinc oxide fume inhalation are mediated by cytokines. To study this hypothesis, we have examined the exposure–response relationship between zinc oxide exposure and human health effects, 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.

Objectives

Inhalation of zinc oxide fume causes a syndrome consisting of fever, malaise, and leukocytosis known as "Metal Fume Fever" (MFF). Study Hypotheses are: (1) MFF is a systemic response to zinc oxide fume inhalation that results from the synthesis and release of cytokines acting as chemotactic factors and as endogenous pyrogens. One manifestation of the zinc oxide 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 zinc oxide fume inhalation. Elucidating the mechanism of zinc oxide's effect will address a group of illnesses representing an important clinical problem in occupational medicine. Furthermore, zinc oxide 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.

Methodology

We have studied subjects who perform electric welding on galvanized materials. Exposures are carried out within a specially designed environmental chamber. Personal breathing zone air sampling data provides an assessment of the level of exposure experienced. We measure pulmonary function and airway responsiveness to methacholine at baseline and again 1 hour and either 6 or 20 hours following exposure. We then 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 interleukin (IL)–1, IL–4, IL–6, IL–8 and TNF. In addition, we have carried out pilot in vitro studies with human pulmonary macrophages from normal subjects without zinc oxide exposure. We have exposed macrophages to low levels of zinc oxide in vitro, using titanium oxide as a negative control and lipopolysaccharide (LPS) as a positive control.

Significant Findings

We carried out 26 experimental welding exposures in 23 volunteer subjects, performing post–exposure bronchoalveolar lavage (BAL) 3 hours (n = 6), 8 hours (n = 11), or 22 hours (n = 9) after exposure. We initially analyzed the first 14 subjects. Subjects with the highest cumulative exposures all experienced typical MFF symptoms. We showed that overall, the changes in pulmonary function and reactivity at one, six and 20 hours were minimal. Moreover, there was no statistically significant correlation between cumulative zinc exposure and the minimal changes observed, including a 7% fall in DLco, the greatest change seen. Bronchoalveolar lavage fluid at 22 hours in the late follow–up group yielded numerous polymorphonuclear leukocytes with a strongly positive correlation between cumulative zinc oxide welding fume exposure and polymorphonuclear leukocyte concentrations both at 8 and 22 hours follow–up. These initial data demonstrated that zinc oxide welding fume inhalation

is associated with a dose–dependent, marked inflammatory cellular response in the lung whether or not clinical symptoms of metal fume fever were reported. We then carried out further analysis and have submitted for publication further analysis of cytokine analysis from all 26 exposures. We detected tumor necrosis factors (TNF), interleukin–6 (IL–6) and interleukin–8 (IL–8) varying in a time– and exposure–related manner. The concentration of TNF in the BAL fluid supernatant was significantly greater at 3 hours than at 8 or 22 hours after exposure ($p<0.05$), exhibiting a statistically significant exposure–response relationship to airborne zinc at each follow–up time period ($p<0.05$). TNF concentrations were statistically correlated with those of IL–6 in BAL supernatant obtained at 22 hours ($r=0.78$, $p=0.01$) and with concentrations of IL–8 in BAL 8 hours after exposure ($r=0.85$, $p=0.001$). IL–6 displayed a significant exposure–response relationship to zinc ($p<0.05$) at 22 hours. IL–8 exhibited a significant exposure–response relationship to zinc ($p<0.05$) at 8 hours after exposure, a time at which IL–8 correlated with marked increases in BAL fluid polymorphonuclear leukocytes (PMNs) ($r=0.7$,$p=0.01$). Although we also detected interleukin–1 (IL–1) in BAL samples, this cytokine did not demonstrate a statistically significant exposure–response. TNF, IL–6 and IL–8 in BAL fluid supernatant concentrations increased in a time and exposure–dependent fashion after zinc oxide welding fume exposure. The time course of increased cytokines, their correlations with one another and with PMNs in the BAL fluid, and the consistency of our findings with the known kinetics and actions of these cytokines support the hypothesis that a network of cytokines is involved in the pathogenesis of metal fume fever.

We have also studied a "positive control" group consisting of exposures to moldy wood chips. This exposure is associated with a syndrome clinically similar to metal fume fever. Our studies in this area are preliminary, but also suggest a role for cytokines. In total we have studied six subjects after such exposures: four subjects at 22 hours follow–up; and one each at 3 and 8 hours. Among the 22 hour group we have observed a marked increase in PMNs in BAL; in three of these subjects control BAL without preceding exposure has been without any increased PMNs.

Pilot in vitro exposure of human pulmonary macrophages has demonstrated an increase in TNF in supernatant media as early as three hours post initiation of exposure. A similar response has not been observed with titanium. We intend to continue this in vitro work, including study in other animal models and delineation of other cytokines relevant to potential interactions of interest (cytokine networking).

Publications

Blanc PD, Schwartz DA: Acute Pulmonary Responses To Toxic Exposures. In: Textbook of Respiratory Medicine, 2nd edition, (eds. JF Murray, JA Nadel), WB Saunders, in press, 1993

Blanc PD, Boushey HA, Wong H, Wintermeyer SF, Bernstein MS: Cytokines in Metal Fume Fever. Am Rev Respir Dis 147:134–139, 1993

Wintermeyer SF, Wong H, Blanc PD: Bronchoalveolar Lavage Fluid Interleukin–6 in Human Subjects Exposed To Organic Dust. Amer Rev Respir Dis 147:A527, 1993

Wintermeyer SF, Wong H, Blanc PD: Lymphocyte Subsets in Bronchoalveolar Lavage Fluid After Zinc Oxide Welding Fume Inhalation in Human Subjects. Clin Res 41:32A, 1993

Blanc PD, Boushey HA: The Lung in Metal Fume Fever. Semin Respir Med, in press 1993

Blanc PD, Boushey HA, Wintermeyer S, Wong H, Bernstein M: Bronchoalveolar Lavage Fluid Tumor Necrosis Factor After Zinc Oxide Fume Inhalation in Human Subjects. Am Rev Respir Dis 145:A795, 1992

Blanc PD, Boushey HA, Wintermeyer S, Wong H, Bernstein M: Bronchoalveolar Lavage Fluid Interleukin–8 After Zinc Oxide Welding Fume Inhalation in Human Subjects. Clin Res 40(1):67A, 1992

Blanc P, Boushey HA: Metal Fume Fever: Specific Clues to Making the Diagnosis. J Respir Dis 13:15–26, 1992

Conrad DJ, Warnock M, Blanc P, Cowan M, Golden JA: Micrograniulomatous Aspergillosis after Shoveling Wood Chips. Am J Ind Med 22:411–418, 1992

Blanc P, Wong H, Bernstein MS, Boushey HA: An Experimental Model of Metal Fume Fever. Ann Int Med 114:930–936, 1991

Asbestos-Induced Pleural Fibrosis and Lung Restriction

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Grant Number: *5 K01 OH00093-03*
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Funding Level: *$0 ($122,514 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 were 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 sub radiographic 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 International Labor Organization, 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 International Labor Organization to 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. In addition, we will use computer–assisted methods to identify and quantify the extent of pleural disease on the CT scan.

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. In addition, we will use computer–assisted methods to identify and quantify the extent of pleural and parenchymal disease on the CT scan.

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 the 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 forced vital capacity (FVC). No significant relationship was observed between FVC and either diaphragmatic plaques or pleural calcifications. However, since the pleural abnormalities are highly collinear, 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 dyspnea. 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.

To identify the determinants of dyspnea and evaluate the validity of this subjective measure, we compared dyspnea assessments to objective measures of lung disease in workers exposed to asbestos. Our study population consisted of 78 asbestos–exposed workers, 23 with a normal chest radiograph (CXR), 43 with pleural fibrosis, 27 with asbestos is, and 16 with both pleural fibrosis and asbestos is. Assessments of dyspnea, by categorical measurements, were performed by one observer who was blinded to all other clinical information. Dyspnea classes ranged from I to V with class I being dyspnea at an activity level appropriate to elicit dyspnea in normal subjects and class V being dyspnea with minimal activity or at rest. Subjects had full pulmonary function tests (PFT), a complete cardiopulmonary exercise test, a measurement of lung compliance, a CXR, and a high resolution CT (HRCT) scan. In our study population 35 subjects had class I dyspnea, 21 subjects had class II dyspnea, 6 subjects had class III dyspnea, 10 subjects had class IV dyspnea, and 6 subjects had class V dyspnea. Dyspnea classes were collapsed into fewer classes when needed to facilitate statistical analysis. PFT data showed significant associations between increases in dyspnea class and decreases in percent predicted total lung capacity (p=0.007), forced vital capacity (p=0.002), forced expiratory volume at 1 second (p=0.002), and decreases in absolute maximum voluntary ventilation (MVV) (p=0.02). Increasing dyspnea was also found to be marginally associated with decreases in percent predicted diffusion capacity of carbon monoxide (p=0.06). Cardiopulmonary exercise data showed significant associations between increases in dyspnea class and both decreases in oxygen consumption per kilogram of body weight at maximum exercise (VO2 Max/kg) (p=0.005) and increases in heart rate reserve at maximum exercise (p=0.02). In addition, increasing dyspnea was marginally associated with decreases in breathing reserve at maximum exercise (p=0.08). Decreased expiratory lung compliance at 60 percent of total lung capacity tended to be associated with increasing dyspnea (p=0.07). No consistent association was identified between dyspnea class and abnormalities on either the CXR or the HRCT scan. These results indicate that dyspnea is related to several objective measures of lung disease among workers exposed to asbestos. In particular, we found that dyspnea is associated with reduced lung volume and decreased exercise tolerance. These findings suggest that dyspnea is a valid measure of impaired lung function in asbestos–exposed workers.

To assess the clinical significance of asbestos–induced pleural fibrosis on exercise physiology, we evaluated the relationship between radiographic evidence of pleural fibrosis and physiologic results from cardiopulmonary exercise testing in 90 asbestos–exposed subjects. A bicycle ergometer was used to measure the cardiac and pulmonary response to maximal exercise. Eight subjects were found to have an abnormal cardiac response to exercise (6 unstable blood pressure and 2 ischemic electrocardiogram) and these individuals were excluded from further analysis. Of the remaining 82 subjects, 47 (57%) had pleural fibrosis. Of those with pleural fibrosis, 33 (70%) had circumscribed pleural plaques and 14 (30%) had diffuse pleural thickening involving the costophrenic angle. Interstitial fibrosis (ILO $\geq$ 1/0) was present in 40% of those with normal pleural, 39% of those with circumscribed pleural plaques, and 14% of those with diffuse pleural thickening. Pleural fibrosis was found to be significantly associated with older age, a lower baseline maximal voluntary ventilation, and a lower percent predicted total lung capacity. Although pleural fibrosis did not appear to be related to impaired respiratory function with exercise in our entire cohort, this finding was confounded by a higher proportion of interstitial fibrosis in subjects with normal pleura. In fact, among study subjects without asbestos is, significant decreases in gas exchange (higher VD/VT and increased A–a O_2 difference) were observed at maximal exercise among subjects with pleural fibrosis. Interestingly, neither a high respiratory rate nor a lower VT/FVC ratio was observed among those with pleural fibrosis indicating that pleural fibrosis alone does not explain the increased VD/VT. Using multi variate analyses to control for potential confounders (age, height, weight, smoking history, pack–years of smoking, and ILO profusion category), regression models demonstrated that pleural plaques and diffuse pleural thickening were independently associated with significant

increases in dead space ventilation (VD/VT) with maximal exercise. These findings indicate that asbestos–induced pleural fibrosis is independently associated with decrements in gas exchange with maximal exercise and suggest that interstitial lung disease, not detected on the routine chest x–ray, may be responsible for this abnormal response to exercise.

Traditional radiological methods to assess the extent and severity of interstitial lung disease have proved imprecise and unreliable. Moreover, considerable intra– and inter–observer variability exist using the ILO classification system to assess the interstitial changes on the chest x–ray. To improve the reliability of the radiographic assessment of interstitial lung disease, we developed and tested a computer assisted method to analyze the lung parenchyma imaged on the high resolution CT (HRCT) scan. We have analyzed full chest HRCT scans of 60 subjects with extensive occupational asbestos exposure and 24 subjects with idiopathic pulmonary fibrosis (IPF). The images from the lung parenchyma were used to construct a gray scale histogram standardizing the density of air in the trachea to a value of –1000 and the column of blood in the aorta to a value of zero. The gray scale histogram in both groups of study subjects has a skewed, unimodal distribution. However, when compared to the asbestos–exposed subjects, the patients with IPF had a gray scale distribution that was shifted to the right and was flatter (lower kurtosis).

	Abestos Exposed	IPF	P Value
	(n=60)	(n=24)	
Gray Scale Intensity			
Mean	–825.20±32.3	–749.10±53.9	<0.001
Median	–877.70±28.0	–811.60±53.7	<0.001
Kurtosis	7.63±2.35	2.56±2.01	<0.001
Skewness	2.63±0.37	1.57±0.46	<0.001

Limiting the analysis to study subjects with category 1 ILO chest films, patients with IPF appeared to have more abnormal gray scale densities than those with asbestos is. However, in a multi variate analysis after controlling for age and cigarette smoking, we found that the mean and median gray scale density were independently related to total lung capacity, the concentration of eosinophils in the bronchoalveolar lavage fluid, the ILO category on chest x–ray, and the presence of moderate to severe dyspnea. Importantly, these factors accounted for 65% of the variance of the mean and 63% of the variance of the median gray scale density. Moreover, once these factors were accounted for, no differences in gray scale measures were noted between IPF and asbestos is. These findings indicate that computer derived measures of interstitial lung disease appear to be clinically meaningful and may overcome the well documented problem of subjective radiological interpretation. We anticipate that this approach may provide useful information regarding interstitial lung disease which will complement the traditional measures currently used to assess disease extent and severity.

To further assess the clinical significance of asbestos–induced pleural fibrosis, we used a computer algorithm to three–dimensionally reconstruct images from the high resolution computerized tomography (HRCT) scan of the chest in 60 asbestos–exposed study subjects. The study subjects had been occupationally exposed to asbestos at least 20 years prior to this investigation and were on average 62 years of age. Pulmonary function tests, chest radiographs, and HRCT scans were performed on all study subjects. Thirty–five (58.3%) had pleural fibrosis and 19 (31.7%) had asbestosis (ILO 2 ≥ 1/0) identified on the chest radiograph. The volume of asbestos–induced pleural fibrosis was computed from the three–dimensional reconstruction of the HRCT scan and among those with pleural fibrosis identified on the HRCT scan (N=29), the volume of the pleural lesion varied from 0.5 ml to 260.4 ml or between 0.01% and 7.11% of the total chest cavity. To assess the validity of these computer–derived estimates, we compared the computer derived estimates of parenchymal volume to those independently obtained by pulmonary function testing. Importantly, the three–dimensional computer–derived estimate of lung volume was found to be significantly associated with the independent measurement of total lung capacity (r=.46; P=0.0001). To investigate the relationship between asbestos induced pleural fibrosis and restrictive lung function, we compared the computer–derived estimate of pleural fibrosis to the total lung capacity and found that these measures were inversely related (r=–.40; P=0.002). After

controlling for age, height, pack–years of cigarette smoking, and the presence of interstitial fibrosis on the chest radiograph, the volume of pleural fibrosis identified on the three–dimensional reconstructed image from the HRCT scan was inversely associated with the total lung capacity (P=0.03) and independently accounted for 9.5% of the variance of this measure of lung volume. These findings further extend the scientific data supporting an independent association between pleural fibrosis and restrictive lung function.

To prospectively identify the determinants of progressive loss of lung function among workers occupationally exposed to asbestos and assess the relative contribution of cigarette smoking, asbestos–induced pleural fibrosis, and findings from bronchoalveolar lavage and the high resolution CT scan, we examined the determinants of lung function changes in 117 subjects occupationally exposed to asbestos. All subjects had been occupationally exposed to asbestos for at least one year in a high exposure setting and a minimum of 20 years was required between the first exposure to asbestos and entry into the study. Baseline studies included an independent assessment of dyspnea, lung volumes, diffusing capacity of carbon monoxide (Dl_{CO}), a chest radiograph, a high resolution CT (HRCT) scan, and bronchoalveolar lavage. Our subjects were observed for an average of two years (range 0.5 years to 4.0 years) and lung function was measured on at least two separate occasions (mean=4.1 separate tests). During the period of observation, there was an average 1.5% decrease (range=loss of 27% to an increase of 39%) in the total lung capacity (TLC) and a 2.5% decrease (range=loss of 30% to an increase of 39%) in the diffusing capacity of carbon monoxide (Dl_{CO}). After controlling for age, height, pack–years of cigarette smoking, and follow–up time, longitudinal declines in TLC were independently related to moderate to severe dyspnea (P=0.005), diffuse pleural thickening (P=0.007), and higher concentrations of fibronectin in the BAL fluid (P=0.01). Interestingly, interstitial lung disease either on the chest radiograph or HRCT scan was not independently associated with longitudinal changes in TLC. After controlling for age, height, and follow–up time, longitudinal declines in Dl_{CO} were independently related to moderate to severe dyspnea (P=0.006), increased pack–years of cigarette smoking (P=0.00001), honeycombing on HRCT scan (P=0.0009), and higher concentrations of lymphocytes (P=0.0008), neutrophils (P=0.0005), eosinophils (P=0.03), and fibronectin (P=0.02) in the BAL fluid. These results indicate that among asbestos–exposed subjects, prognostically important risk factors include symptoms of dyspnea, cigarette smoking, diffuse pleural thickening, honeycombing on HRCT scan, and higher concentrations of inflammatory cells and fibronectin in the BAL fluid. Moreover, these risk factors could be used to identify high risk asbestos–exposed workers who would be ideal candidates for innovative, disease modifying drug regimens.

Publications

Hartley PG, Galvin JR, Hunninghake GW, Merchant JA, Yagla SJ, Speakman SB, Schwartz DA: High Resolution CT–derived Measures of Lung Density Are A Valid Index of Interstitial Lung Disease. J App Physiol, in press, 1993

Shih JF, Wilson JS, Broderick A, Watt JL, Galvin JR, Merchant JA, Schwartz DA: Asbestos–Induced Pleural Fibrosis and Impaired Exercise Physiology. Chest, in press, 1993

Schwartz DA, Helmers RA, Galvin JR, Van Fossen DS, Frees KL, Dayton CS, Burmeister LF, Hunninghake GW: Determinants of Survival in Idiopathic Pulmonary Fibrosis. Am Rev Respir Dis, in press, 1993

Blanc PD, Schwartz DA: Acute Pulmonary Response to Toxic Exposure. In: Textbook of Respiratory Medicine, (eds. JF Murray, JA Nadel), W.B. Saunders Co., Philadelphia, in press, 1993

Schwartz DA: Chemical Injury to the Lung. In: Textbook of Clinical Occupational and Environmental Medicine, (eds. L Rosenstock, M Cullen), W.B. Saunders Co., Philadelphia, in press, 1993

Clapp WD, Thorne PS, Frees KL, Zhang X, Lux CR, Schwartz DA: The Acute Effects of Inhalation of Grain Dust Extract and Endotoxin on Upper and Lower Airways. Chest 104:825–830, 1993

Schwartz DA, Redlich CA: Biomarkers in Occupational Lung Disease. Sem Respir Med 14:167–180, 1993

Schwartz DA, Galvin JR, Frees KL, Dayton CS, Burmeister LF, Merchant JA, Hunninghake GW: The Clinical Relevance of Cellular Mediators of Inflammation in Workers Exposed to Asbestos. Am Rev Respir Dis 148:68–74, 1993

Shih JF, Hunninghake GW, Goeken NE, Galvin JR, Merchant JA, Schwartz DA: The Relationship Between HLA–A, B, DR Antigens and Asbestos–induced Lung Disease. Chest 104:26–31, 1993

Schwartz DA, Galvin JR, Yagla SJ, Speakman SB, Merchant JA, Hunninghake GW: Restrictive Lung

Function and Asbestos–induced Pleural Fibrosis: A Quantitative Approach. J Clin Invest 91:2685–2692, 1993

Pueringer RJ, Schwartz DA, Dayton CS, Gilbert SR, Hunninghake GW: The Relationship Between Alveolar Macrophage TNF, IL–1, and PGE_2 Release, Alveolitis, and Disease Severity in Sarcoidosis. Chest, in press, 1992

Dayton CS, Schwartz DA, Helmers RA, Pueringer RJ, Gilbert SR, Merchant RK, Hunninghake GW: Outcome of Subjects with Idiopathic Pulmonary Fibrosis Who Fail Corticosteroid Therapy – Implications for Further Studies. Chest, in press, 1992

Kline JN, schwartz DA, Monick MM, Floerchinger CS, Hunninghake GW: Relative Release of IL–1b and IL–1RA by Alveolar Macrophages in Asbestos–induced Lung Disease, Sarcoidosis, and Idiopathic Pulmonary Fibrosis. Chest, in press, 1992

Schwartz DA, Landas SK, Burmeister LF, Hunninghake GW, Merchant JA: Airway Injury in Swine Confinement Workers. Ann Intern Med 116:630–635, 1992

Schwartz DA, Galvin JR, Dayton CS, Merchant JA, Hunninghake GW: The Influence of Cigarette Smoking on Bronchoalveolar Lavage Cellularity in Asbestos–induced Lung Disease. Am Rev Respir Dis 145:400–405, 1992

Broderick A, Fuortes LJ, Merchant JA, Galvin JR, Schwartz DA: The Pleural Determinants of Restrictive Lung Function and Respiratory Symptoms in an Asbestos–exposed Population. Chest 101:684–691, 1992

Schmidt LE, Thorne PS, Watt JL, Schwartz DA: Is an Abbreviated Bronchial Challenge with Histamine Valid? Chest 101:141–145, 1992

Merchant RK, Schwartz DA, Helmers RA, Dayton CS, Hunninghake GW: Bronchoalveolar Lavage Cellularity: The Distribution in Normal Volunteers. Am Rev Respir Dis 146:448–453, 1992

Hempel SL, Schwartz DA, Hunninghake GW: The Mast Cell and Idiopathic Pulmonary Fibrosis. Mayo Clin Proc 67:1009–1010, 1992

Broderick A, Schwartz DA: Halogen Gases, Ammonia, and Phosgene. In: Medical Toxicology of Hazardous Materials, (ed. JB Sullivan, Jr.), Williams & Wilkins, Baltimore, pp. 791–796, 1992

Merchant JA, Schwartz DA: Classification of the Chest Radiograph and CT Scan for the Pneumoconioses. In: Environmental and Occupational Medicine, (ed. W Rom), Little, Brown, Boston, MA, pp. 215–225, 1992

Schwartz DA: Effects of Dusts, Fumes, and Other Inhaled Substances. In: Foundations of Respiratory Care, (eds. DJ Pierson, CV Spearman, RM Kacmarek), Churchill Livingstone, Inc., pp. 365–369, 1992

Schwartz DA: Effects of Smoking on the Cardiorespiratory System. In: Foundations of Respiratory Care, (eds. DJ Pierson, CV Spearman, RM Kacmarek), Churchill Livingstone, Inc., pp. 359–364, 1992

Schwartz DA: Asbestos–induced Lung Disease: A Model Approach to Pneumonoconioses. Immunology and Allergy Clinics of North America, (ed. EJ Bardana, Jr.), W.B. Saunders Co., Philadelphia, 12:847–859, 1992

Merchant JA, Schwartz DA: Occupational Parenchymal Disease. In: Textbook of Internal Medicine, (ed. WN Kelley), J.B. Lippincott Co., Philadelphia, pp. 1753–1759, 1992

Schwartz DA: The Clinical Relevance of Asbestos–Induced Pleural Fibrosis. Ann N Y Acad Sci 643:169–177, 1991

Landas SK, Schwartz DA: Mica–associated Pulmonary Interstitial Fibrosis: A Case Report. Am Rev Respir Dis 144:718–721, 1991

Schwartz DA, Dayton CS, Hunninghake GW: The Clinical Utility and Reliability of Asbestos Bodies in Bronchoalveolar Fluid. Am Rev Respir Dis 144:684–688, 1991

Schwartz DA, Helmers RA, Dayton CS, Merchant RK, Hunninghake GW: Determinants of Bronchoaveolar Lavage Cellularity in Idiopathic Pulmonary Fibrosis. J Appl Physio 71(5):1688–1693, 1991

Schwartz DA, Merchant RK, Helmers RA, Gilbert SR, Dayton CS, Hunninghake GW: The Influence of Cigarette Smoking on Lung Function in Patients With Idiopathic Pulmonary Fibrosis. Am Rev Respir Dis 144:504–506, 1991

Schwartz DA: New Developments in Asbestos–Induced Pleural Disease. Chest 99:191–198, 1991

Grain Dust Exposure: Physiologic & Biologic Correlates

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Importance to Occupational Safety and Health

Inhalation of grain dust is associated with acute and chronic airflow limitation, as well as inflammation of the lower respiratory tract. There are a large number of workers who are exposed to levels of grain dust that are considered to be harmful. Furthermore, there is evidence that a variety of host factors such as atopy, asthma, ethnic background, age, and smoking, modulate the physiologic (airflow) response to inhalation of grain dust. Little work has been done investigating the inflammatory response.

By characterizing the physiologic as well as the inflammatory responses further, insight will be gained into the extent to which these host factors modulate the response to inhaled grain dust. Furthermore, the effects of a variety of interventions (physical manipulation of the environment to pharmacologic methods) can be explored. In this way, groups of workers at greater or lesser risk for disease, as well as preventive measures can be defined.

Objectives

1. Inhalation of aqueous grain dust extract causes inflammation primarily localized to the airways, and is associated with airflow obstruction.
2. Host factors, such as age, ethnic background, gender, atopic status, asthma, and cigarette smoking modulate the duration, intensity and severity of these effects.
3. Repeated exposure results in physiologic and biologic tolerance occurring within days of onset of exposure. This tolerance is modulated by one or several host factors which will be investigated in objective 2 above.

Methodology

Using aqueous extracts of grain dust, subjects will undergo inhalation challenge followed by pulmonary function testing to assess the physiologic effects of the inhalation of the extract, then bronchoscopy, to collect specimens from the airways and alveoli for examination of the inflammatory response. Specimens will be evaluated at the cellular, biochemical and molecular level, to find sensitive and specific markers of inflammation that can be used to characterize the inflammatory response. Subjects endowed with different host factors will then be tested and compared to control subjects. The presence of tolerance will be assessed using repeated inhalation challenge.

Significant Findings

None to date.

Radon, Bronchial Morphometry, and Occupational Health

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Importance to Occupational Safety and Health

The hazards of occupational exposure to radon daughters relative to environmental exposure is significant both for occupational and environmental health. Much attention has been paid to relative physical factors (bronchial epithelial dose/WLM) in the two situations, but almost no attention to the relative biological factors (risk/unit bronchial dose in miners vs. general public). These biological differences arise because of the (average) thicker mucosal layers in the 70% of miners who smoke, compared to the ~70% of the general public who do not smoke. Preliminary calculations for a single biological endpoint suggest that this biological factor may differ by about a factor of two between miners and the general public, which would be larger than

any physical differences in dose per unit WLM exposure.

Objectives

The aim of this small grant pilot study is to produce evaluations of the relative biological hazards of radon daughters per unit lung dose, for pertinent biological endpoints, for miners vs. envirommentally–exposed home residents.

Methodology

In particular, it is proposed to (1) analyze previously–collected biological data to quantify how the relative biological hazard varies with LET (Linear Energy Transfer, or stopping pow or, dE/dx) and its microdosimetric correlate, lineal energy. Only biological measurements pertinent to risk estimation, namely oncogenic transformation, mutation, and chromosomal damage, will be considered; (2) use Monte–Carlo simulation of alpha–particle transport together with the best available data on mucosal and epithelial thicknesses in smokers and nonsmokers, to estimate the energy deposition characteristics of the radon–daughter alpha particles in the cells at risk in the bronchial epithelia of miners and the general public; (3) combine the data from (1) and (2) to obtain relative biological risk factors for occupational miners and the general public.

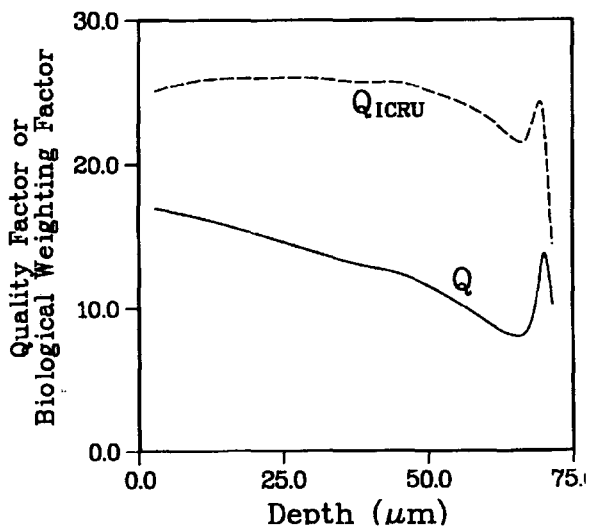
Significant Findings

A large body of new biophysical data, measured in our laboratory using the C3H10Tl/2 *in vitro* oncogenic transformation system, has been analyzed. This new data set is by far the most complete quantitative data set for an oncogenic transformation end point, as a function of LET and dose, currently available. The data consist of results at 12 LET Is varying from 3 to 475 keV/micron, and an average of 8 low–dose points per LET. The lower curve in the Figure shows the resulting quality factor for radon daughters, as a function of depth from the radon–daughter sources, in the bronchial epithelium.

We have drawn the following conclusions from the analysis of these data:

1. The quality factor for radon is less than the values of 20–30 suggested by the ICRU and ICRP. This is because many of the energy depositions are taking place in the alpha–particle energy region where the biological effect is saturating, i.e. there is an "overkill" phenomenon.
2. Specifically, if target cells are distributed throughout the whole bronchial epithelium, the doseweighted quality factor (biological weighting factor) would be about 15. If, on the other hand, the target cells are only basal cells, the mean quality factor would be 50% less, i.e. around 11.
3. If miners have an extra mucosal layer of ~20 microns in depth, and the target cells are basal cells, the quality factor would be expected to be around 9.

The importance of these biological weighting factors is that they provide the link between radon risk estimates obtained from analysis of survivors at Hiroshima and Nagasaki, with risk estimates obtained from miner studies. When quality factors of ~20–30 have been applied to A–bomb based risk estimates, the resulting risk estimates have been inconsistent with (higher than) those derived from miners. A basis for lower quality factors, provided here, would therefore tend to reconcile radon risk estimates from the two disparate sources.



Publications

Brenner DJ: The Significance of Dose Rate in Assessing the Hazards of Domestic Radon Exposure. Health Physics, accepted, 1993

Brenner DJ, Hall EJ, Randers–Pehrson G, Miller RC: Model Considerations on the Dose–Rate/LET Dependence of Oncogenic Transformation by Charged Particles. Radiation Research 133:3365–369, 1993

Protein Damage Caused By Occupational Toxicants

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Importance to Occupational Safety and Health

Occupational toxicants are potentially capable of producing free radicals in biological systems which can lead to oxidative stress. There are numerous oxidants encountered in occupational environments which may lead to this damage. These include metals, pesticides, volatile organic compounds, ozone, and components of environmental tobacco smoke. One technique which is useful in the assessment of oxidative stress is the monitoring of protein oxidation. Oxidative damage to proteins has been shown to result in increased protein turnover, decreased enzymatic function, and has been associated with a number of pathological processes, including emphysema, atherosclerosis, and neurological diseases.

We are utilizing protein oxidation as a biomarker for oxidant exposure. Levels of oxidized proteins are increased during conditions of oxidative stress, as occurs from occupational exposure to toxicants. This project addresses a significant gap in the literature because there are currently no antibody techniques available for the study of protein oxidation. This project will develop a method to selectively analyze oxidized proteins in a complex mixture of oxidized and non–oxidized proteins, and to assess oxidative stress in a reliable and noninvasive manner. The development of a sensitive measure of protein oxidation using polyclonal antibody techniques will be a major addition to the area of oxidative damage. This will be particularly important in the area of occupational exposure, due to the long potential exposure times to oxidants and the susceptibility of lung to oxidant damage. The polyclonal antibody technique will be a powerful tool which will have tremendous applicability in exposure assessment. This project will provide information that may lead to development of a simple, inexpensive immunoassay that can be utilized to monitor the effects of exposure to oxidants in occupational environments.

Objectives

This project examines the hypothesis that certain occupational toxicants are capable of causing tissue damage by oxidatively modifying proteins and that these oxidized proteins can be detected using polyclonal antibody techniques to provide a measure of exposure assessment. The research plan includes the following two objectives:

Objective 1. To develop an immunochemical assay to detect oxidative protein damage using a polyclonal antibody assay and validate the assay by direct comparison with the established spectrophotometric techniques.

Objective 2. To test the utility of the immunoassay to detect oxidized proteins in animals exposed to oxidants found in occupational environments.

Methodology

These experiments to complete objective 1 will directly compare the spectrophotometric 2,4–dinitrophenylhydrazine technique with the polyclonal antibody technique. Purified protein preparations and tissue fractions will be oxidized using three *in vitro* free radical generating systems. These include exposing the proteins to radiation damage, metal–ion–catalyzed free radical damage, and to an enzymatic free radical generating system consisting of xanthine/xanthine oxidase. In addition to validating the assay, we will determine a quantitative assessment of the sensitivity of the technique. Carbonyl content will be determined spectrophotometrically by reaction with 2,4–dinitrophenylhydrazine and subsequent absorbance determination.

An immunochemical assay will be developed to detect proteins oxidized by chemicals found in occupational environments. The general principle of the assay is similar to the spectrophotometric method for the detection of oxidized proteins except the dinitrophenol group will be detected using an specific antibody. Briefly, proteins from tissue homogenates or fractions will be separated using SDS/PAGE then transferred to nitrocellulose paper (Western blot). The separated proteins will be treated with 2,4–dinitrophenylhydrazine. The nitrocellulose is immunochemically stained with polyclonal rabbit anti–dinitrophenol, and the staining intensity detected using an alkaline phosphatase based detection system or a system based on enhanced chemiluminescence.

The experiments in objective 2 will test the utility of the immunoassay to detect oxidized proteins in animals exposed to oxidants found in occupational

environments, and we will use the model lung toxicant paraquat. We will determine both dose dependent and time course of carbonyl formation *in vivo*.

Significant Findings

We have successfully developed the immunochemical assay for the detection of carbonyl groups generated by *in vitro* methods on purified proteins. The technique has been shown to be significantly more sensitive than the spectrophotometric method.

Role of Worksite-Associated Vanadium in Immunomodulation

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Importance to Occupational Safety and Health

The knowledge gained from the proposed studies, while helping overall to clarify the mechanisms of vanadium–induced immunomodulation, will ultimately contribute to the determination (or revision) of minimal acceptable exposure levels for vanadium in the workplace. As macrophages represent the primary mediators of pulmonary immunocompetence, the mechanisms by which this particular pollutant (in both a soluble and insoluble form) alters macrophage biochemistry with respect to immunoregulating cytokines may also provide a model by which other potential workplace toxicants act in exposed workers. By defining the possible mechanism(s) by which immune responses can be affected by workplace contaminants, such as the vanadium oxides, more accurate assessments of their potential immunotoxicity can be made and proper steps can be taken to minimize the risk from exposure.

Objectives

Several epidemiological studies and our previous *in vivo* laboratory studies have indicated a marked increase in host susceptibility to bacterial/viral diseases after vanadium exposure. Our earlier work determined that following host exposure to vanadium, there is a failure in the ability of resident macrophages to become fully activated for participation in host antibacterial responses. We hypothesized that this reduction in the macrophage capacity to become fully activated is, in part, a result of altered macrophage production, binding, and/or processing of autocrine/lymphokine interferons (IFNα and γ). The specific aims of this project are: (1) to assess the levels of inducible IFNα and IFNγ produced by pulmonary macrophages (PAM) (and other lung accessory cells) found in the intact rat lung after inhalation of occupationally–relevant concentrations of vanadium (in soluble and insoluble forms), (2) to determine whether inhaled vanadium alters PAM surface IFN receptor expression and/or IFN binding, the intracellular delivery and subsequent dissociation of the receptor–IFN complex, and/or the recycling/*de novo* synthesis of surface IFN receptors, and (3) to relate any changes in these measured parameters to overall changes in PAM responsiveness to exogenous IFN, i.e., IFN–induced expression of Class II MHC surface antigens and enhanced production of reactive oxygen intermediates.

Methodology

Male Fisher 344 rats are exposed (nose–only) to atmospheres containing either soluble ammonium metavanadate (NH_4VO_3) or insoluble vanadium pentoxide (V_2O_5) at concentrations found in work environments where vanadium levels are at OSHA permissible levels (0.05 mg V_2O_5/m_3). Control rats receive either air only or inert latex particles of the same mass median diameter as the vanadium–generated particles. Respirable/penetrable (< 1 μm) V_2O_5 atmospheres are generated using a Wright dust feeder, while soluble NH_4VO_3 atmospheres are generated with a Laskin aerosolizer. All rats are exposed for 8 hr/day for 4 days in order to approximate the maximal levels of exposure encountered by workers in an average workweek. One day after the final exposure, the rats are either inoculated intranasally with viable Sendai virus to induce IFN production, or sacrificed and the lung macrophages harvested (by serial lavage) for use in all IFN binding/processing/responsiveness experiments.

IFN analyses: All harvested IFN (IFNα, β, γ mixture) are separated from one another by chemical/physical removal prior to quantitation in a viral

cytotoxicity reduction assay using rat kidney fibroblast cells.

IFN Receptor Binding and Expression: To assess the levels and strengths of IFN receptor binding, radioiodinated IFN is used in both a saturation and competitive binding study with the harvested PAM. Scatchard analyses are used to estimate both the strength of binding (K_d) and the relative numbers of surface receptors present on the target cells. To more accurately assess IFN receptor expression, FACS analyses of the cells tagged with FITC–labeled anti–IFN–receptor monoclonal antibodies is performed.

Receptor Internalization, IFN Release and Degradation: The kinetics of IFN–receptor complex internalization are determined using selective stripping of the non–internalized complexes from the surface of the PAM. To monitor changes in the release of the internalized IFN from its receptor complex, the cells are lysed at fixed intervals and the receptor proteins collected by immunoprecipitation. Subsequent separation over PAGE gels and analysis by differential densitometry allows determination of the disappearance of signal from the complex band, a measure of complex dissociation. To assess the status of the intracellular IFN, the lysate proteins are separated without prior modifications over PAGE gels and analyzed by autoradiography. The signal at the region for free IFN is measured (after accounting for the appearance of newly–released IFN by accounting for total free IFN and complex signals) and the kinetics of IFN breakdown determined.

Receptor Recycling/Synthesis: PAM are treated with unlabeled IFN to induce maximal receptor expression and internalization. After stripping the surface of remaining complexes or unused receptors, half of the PAM are treated with cycloheximide to block *de novo* receptor synthesis. All cells are then incubated with radiolabeled IFN and harvested at fixed intervals to monitor IFN binding. The relative increases in binding by cycloheximide–treated cells are indicative of receptor recycling, while in untreated cells, the degree of binding above that accounted for by recycling are indicative of *de novo* synthesis.

IFN–Inducible Responses: PAM are treated with IFN for periods up to 48 hr and then analyzed by FACS for expression of Class II MHC antigens using standard protocols with anti–rat Class II antibodies. Reactive oxygen intermediate (i.e., superoxide anion and hydrogen peroxide) formation by IFN–treated macrophages are assessed using spectrophotometric measurements of the reduction of ferricytochrome c and the oxidation of phenol red by horseradish peroxidase, respectively.

Significant Findings

Difficulties with the proposed exposure system forced a redesign. The fully–functional newly–designed nose–only exposure system has been completed and, following quality assurance testing of sample delivery, initial exposures are now underway. In addition to the proposed endpoints, all tissues from the exposed rats will now be processed by our departmental histopathology core for determination of physical changes within the lung environment following vanadium exposures; attempts will be made to correlate any hystological changes with functional changes. Furthermore, a recently–developed rat lung macrophage line (NR8313.1) is currently being exposed to both vanadium compounds in order to provide possible correlative data for the information obtained in the *in vivo* studies.

Development of Models to Predict Optimal Lifting Motion

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Importance to Occupational Safety and Health

Back injuries due to manual lifting are a serious problem in terms of human suffering and cost. An ergonomic approach to solve the problem is to redesign the lifting tasks to better fit human capabilities. Thus, biomechanical models serves a very useful purpose in analyzing the human motion patterns and estimating the stresses on the musculoskeletal system especially the lumbar spine. With the development of simulation lifting models, it is possible to provide an indirect means of performing the biomechanical analysis without collecting the displacement–time information. The model predicts the motion pattern based on the specified characteristics of anthropometry, of work station, and of lifting task, using optimization techniques.

Objectives

The goal of this study is to develop a biomechanical simulation model which can predict displacement time information for five selected joints during manual lifting. The six selected joints are wrist, elbow, shoulder, hip, knee, and ankle.

Methodology

To accomplish the objective, there are three general tasks to be undertaken. The first task is to generate the possible posture assumed by the joints at each time frame during the lifting course. The second task is to evaluate the kinematics and kinetics of the lifting generated from the first task. Within the two–dimensional space defined by the ankle–origin coordinate system, the lifting motion from the starting posture to the ending posture is computed and mathematically described. The third task is to improve the lifting motion by minimizing an objective function. By considering that different lifting motion patterns have different objective function values, the smallest objective function value within the feasible operation region indicates the best lifting motion pattern.

Significant Findings

The predictions and the actual displacement–time information were compared by closeness (average of the sum of squares of errors) and trend (average of the disconcordant pairs). The model, considering both kinematic and kinetic capabilities, provides promising results. In general, the envelope formed by the predicted motion patterns overlapped with the envelope formed by the actual motion patterns. In addition to the displacement–time plot comparison, model analyses were also carried out by comparing the box and joint trajectories using stick diagram and animated stick motion. Close examination of the predicted trajectory of the box revealed that in some cases the box penetrated through the table. Analyses using data collected on trained subjects showed a significant decreasing trend in the objective function during the training period, which was indicative of the optimization hypothesis of the model. Overall, the analyses showed:

1. The prediction of the box and joint trajectories may violate physical constraints such as object avoidance. New constraints are being developed and evaluated to allow the model to better describe the motion responsible for object avoidance during the lifting course.
2. Phase relationships, evaluated by the disconcordant pairs, can be found in the displacement–time plot comparisons. In most cases, actual displacement arose faster than the prediction in the early stage of the lift. The animated stick motion also showed that the model lagged behind the actual lift at the beginning of the lift.
3. Training data showed that the decreasing trend in objective function was primarily due to the decrease in total lifting time. This may have important implication in accounting for the lag of the prediction as described in 2.

Publications

Bernard TM, Lin CJ, Ayoub MM, Hsiang MS: Predicting the Optimal Lifting Motions Through Simulation, Proc of the M.M. Ayoub Occupational Ergonomics Symposium, pp 97–100, April 16–17, 1993

Ayoub MM, Blair EL, Hsiang S, Chinnam B: Biomechanical Simulation of Lifting. Proc of the

11th Congress of the International Ergonomics Association, Paris, pp 63–65, 1991

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

Cumulative Trauma Disorder: Skeletal Muscle Dysfunction

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Importance to Occupational Safety and Health

Chronic pain originating from the musculoskeletal system is a dominant cause of sick–leave in modern industry and can be very disabling and troublesome for the individual. The cause of this problem as it originates in skeletal muscle is unknown. However, one of the most common situations in which muscle pain is experienced is the cumulative trauma disorder (CTD) which results from repeated movements. One aspect of repeated movements is the necessity for muscles to decelerate the body or moving body part by eccentric muscle actions. During eccentric muscle actions, muscles act as shock absorbers and absorb strain energy. It is during these shock absorption activities that strain injuries occur. We have developed a laboratory model for repeated strain injury in order to study the tissue response and adaptation of muscles subjected to repeated strains. From our initial studies, it was apparent that the overall size of the muscles becomes larger but the individual components are smaller – perhaps in an attempt to distribute the strain over a greater number of functional units. However, this response seems to be dependent on the rate of strain. In addition, the non–muscle tissue of some of these strained muscles proliferates as one might see in scar tissue or dystrophy. This additional non–muscle tissue may: (1) alter the action of muscles as motors decreasing their force or ability to shorten at maximal speeds; (2) decrease their compliance causing connecting structures (e.g., fascia, ligaments, tendons) to be injured. Therefore, the development and characterization of a rodent model of repeated strain injury is necessary for the understanding of the physiology or pathophysiology of cumulative trauma disorder in order to develop preventative strategies.

Objectives

The proposed experiments are designed to develop a reproducible technique for producing chronic overload injury to rat skeletal muscles as a model for cumulative trauma disorder (CTD) and to understand the functional outcome of repeated microtrauma in order to develop strategies and programs for its prevention. The objectives of the study are: (1) to design and build a rodent dynamometer which will control the velocity and range of movement of the rat foot during a strain overload and to test the functional outcome in terms of muscle strength, endurance, and stiffness in vivo; (2) to document changes in the extracellular matrix (ECM) and sarcolemma of skeletal muscles which could lead to microfibrosis, restricted movement or impaired nutrient flow through the interstitial space using morphological and immunochemical analysis; (3) to characterize the cellular responses of muscle and non–muscle cells following repeated injury in order to understand if the adaptation seen following repeated microtrauma is functional (regeneration and repair) or dysfunctional (fibrosis with myofiber atrophy); (4) to determine the parameters most critical to injury production such as velocity of strain, nature of loading (duration), magnitude of force, frequency of injury and rest periods; 5) to develop immunohistochemical markers for myofiber injury and repair.

Methodology

Cumulative microtrauma is administered three times a week for four weeks using our newly constructed rodent dynamometer to one leg of female rats. Muscle weights, myofiber counts and sizes are analyzed from control soleus muscles and injured (CTD) soleus muscles using the image analysis program, OPTIMAS and a unique technique we developed using Kodak Ektachrome slides as the source of the image. Accurate and reproducible fiber

size distributions can now be made without missing very small fibers.

Immunohistochemical markers have been developed to test for injury and repair as follows. Myofiber integrity is monitored by using dystrophin for plasma membrane, fibrinogen for extracellular protein entry, and desmin for cytoskeletal degradation – an early response of injured muscles. Immunohistochemical localization of tenascin and fast myosin proved good indicators of regeneration and have become routine markers.

The extracellular matrix outside that considered the basal lamina appears to proliferate following some types of repeated injury (CTD) – similar to that seen in dystrophic muscles. Increased amounts of proteoglycans, collagens I and III and fibronectin are localized with immunohistochemical techniques in injured muscles along with mast cell proliferation and degranulation. Quantitative ELISAs are midway through development for documenting the extent of this matrix expansion. A few samples have been studied with scanning electron microscopy to determine the nature of attachments between myofibers. These connections seem to have an ultrastructure similar to collagen fibers – absent from control samples. Because of the nature of the sample preparation, it is difficult to maintain the structural integrity and alignment of the fibrous skeleton of the muscle sample. However, the results are better and should be finished this year. It is very important to document these connections because they have tremendous implications for muscle mechanics and the energy cost of simple movements.

In order to understand the physiological significance of the cellular and matrix changes, a dynamometer was needed for the measurement of rat hind–limb muscles *in vivo*. Dynamic movements can now be measured by a motor driven arm which moves the rat foot through a predetermined range of motion while measuring the force exerted on the dorsum of the foot opposing the movement. After much pilot investigation, a protocol for injury and muscle testing has been developed. Briefly, an isovelocity movement at 30 deg/sec is performed only using concentric muscle actions. This test does not in itself injure the muscle as we have demonstrated in humans as well. Subsequently, a series of sinusoidal movements are introduced to the active muscles which produce repeated damage. The isovelocity test is repeated to document any force decrement or material fatigue. Isometric tests are performed to correlate with the type of measurements used by NIOSH in evaluation of human performance.

Significant Findings

Muscle and non–contractile tissue proliferated following repeated strain injury but this response was dependent on the strain rate. If the strains were performed at fast speeds, the size of the myofibers was smaller and there was an increase in fiber number and extracellular matrix content – an appearance often seen in a dystrophic muscle. If the strains were repeated at slower speeds, the muscles hypertrophied with little matrix expansion as seen following exercise training. This unique observation has never been reported before and may provide a key towards prevention. Part of the increase in muscle size in muscles injured by fast strain rates could be accounted for by an increase in extracellular matrix (non–contractile tissue). Increased amounts of proteoglycans, collagens I and II and fibronectin were common features of the injured muscles with an increase of almost 40% as assessed by morphometric methods. In addition, preliminary evidence obtained with scanning electron microscopy revealed attachments between myofibers which were similar to collagen fibers. The implication of these connections is not clear but could result in greater muscle stiffness.

The physiological outcome of such dramatic muscle changes can now be tested on a custom built dynamometer which has provided quantitative evidence for an increased material fatigue following muscle atrophy. Sinusoidal movements such as experienced while using vibrating tools can be applied to active rat muscles *in vivo*. The stretch–shortening cycle of muscles has never been investigated in relationship to the development of muscle damage and CTD.

Publications

Miller GR and Stauber WT: Use of Computer–Assisted Analysis For Myofiber Size Measurements of Rat Soleus Muscles From Photographed Images. J Histochem Cytochem, in press, 1993

Stauber WT: Delayed Onset Muscle Soreness. In: Athletic Injuries and Rehabilitation, (eds. J Zachazewski, D Magee, W Quillen), Saunders, Philadelphia, in press, 1993

Ergonomic Risk Factors and Cumulative Trauma Disorders

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Importance to Occupational Safety and Health

Cumulative trauma disorders (CTDs) are a large, growing and costly problem in industry. The National Institute for Occupational Safety and Health has identified CTDs as among the 10 most significant occupational health problems in the United States. Prevention of occupational injury and disease relies, in part, on promulgation of standards which mandate limits of acceptable exposure to harmful agents in the work place. This approach has been applied successfully with regard to metals, solvents, carcinogens, and other toxins. In the realm of ergonomics, NIOSH has issued guidelines for manual lifting and prevention of low back disorders. Ideally, the foundations of such standards are a quantitative understanding of the relationship of exposure to risk of disease or injury. Generic work standards are needed for prevention of cumulative trauma disorders of the upper extremities, but current scientific knowledge does not permit precise quantification of risk of developing CTDs. The current study is intended to address that need.

Objectives

The overall objective of this cross–sectional investigation is to study jobs and perform medical screening of workers who are at risk of developing upper extremity cumulative trauma disorders (CTDs) with the goal of modeling quantitative dose–response relations between generic job exposures and medical outcomes. Specific objectives include:

1. To identify jobs with at least three levels of repetition and with at least 20 workers in each category in the study plants.
2. To quantitatively assess job exposures for repetitiveness and other factors which are known to be potential risk factors for developing CTDs, including force, mechanical stress, posture, vibration, and temperature extremes.
3. To perform medical screening of subjects/workers that would include: questionnaire surveys (demographic information, pertinent medical history, occupational history, discomfort/symptom survey), standardized physical examinations of the upper extremities, nonaversive quantitative sensory tests of the upper extremities, strength testing, and limited electrodiagnostic testing of the upper extremities.
4. To model relationships between indices of job exposure (e.g. quantitative rating of repetitiveness) and indices of medical outcomes (e.g. symptoms, physical examination findings, quantitative sensory test results, electrodiagnostic test results, and prevalence of specific CTDs) with the goal of developing quantitative, dose–response relationships between job exposures and medical outcomes.
5. To compare the efficacy of the various medical screening techniques employed to detect CTDs (e.g. to compare the predictive value of quantitative sensory scores in the distal upper extremities to electrodiagnostic test results with regard to identification of possible carpal tunnel syndrome).
6. To make specific recommendations to participating plants and workers about how to reduce ergonomic risk factors identified during the course of this investigation. (If this cross–sectional investigation is successful, then the plants/jobs/workers studied would form the basis of a possible follow–up, prospective study whereby one could assess the medical impact of ergonomic interventions made at the conclusion of the initial cross–sectional investigation).

Methodology

This study will use a cross–sectional design comparing the health of workers in jobs that are stratified on different levels of repetition. Jobs will be analyzed for repetitiveness, force, mechanical stress, posture, vibration, and temperature extremes. Workers in these jobs will undergo standardized medical evaluations that will include a questionnaire, physical examination of the upper extremities, quantitative sensory testing, and limited electrodiagnostic studies at the wrists. Exposure–response relationships will be examined through univariate and multivariate analyses. ANCOVA will be used to evaluate personal risk factors and multiple work factors that may be related to CTDs.

Significant Findings

The initial focus of this first year has been on identifying plant sites and jobs that meet the study requirements of having at least three levels of repetition and with at least 20 workers in each repetition category. Plant walk–throughs, job analyses, and medical surveys have been conducted at several locations, but additional ergonomic and medical surveys will need to be completed before analyses can be performed.

Unexpected Trunk Loading Following Seated Vibration

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Importance to Occupational Safety and Health

This work is studying *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 mechanical damage. Proceeding from prior *in vitro* findings of short–column buckling in the lumbar spine following vibration exposure, this proposal is evaluating how the supporting trunk musculature responds to an unexpected load application after a 40–minute load intervention [seated vertical vibration, seated lateral vibration, seated lateral and vertical vibration or sitting still (as a control)]. This will simulate the sudden and unexpected shift of an object in the hands of the car or truck driver who has driven for 40 minutes. Normal walking (as a break) for ten minutes, prior to an unexpected load application, is also being 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

These hypotheses will be tested using a repeated measures analysis of variance:

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 vertical vibration, seated lateral vibration, seated lateral and vertical vibration, or sitting still (as a control)].
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 vertical vibration, seated lateral vibration, seated lateral and vertical vibration, or sitting still (as a control)].
3. A walking break for 10 minutes "resets" the system.

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. Forty subjects will be tested: 20 males and 20 females of whom 30 are normal controls and 10 are diagnosed with "lumbar instability". 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 flex ion load applied to the subject, performed before and after sustained exposure to the specific loading environments.

Significant Findings

None to date.

Publications

Pope MH, Wilder DG: Whole Body Vibration. In: Occupational Musculoskeletal Disorders: Assessment, Treatment and Prevention, (eds. M Nordin, MH Pope, GBJ Andersson), In Press: Mosby Year Book, 1993/1994

Wilder DG, Wasserman DE, Pope MH, Pelmear PL, Taylor W: Occupational Vibration Exposure, Measurement, Standards and Control. In: Physical and Biological Hazards of the Workplace, (eds. P Wald, G Stave), Van Nostrand Reinholdt, New York, NY, in press, June 1994

Wilder DG: The Biomechanics of Vibration and Low Back Pain. American Journal of Industrial Medicine 23(4):577–588, 1993

Quantitative Assessment of Carpal Tunnel Syndrome

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Importance to Occupational Safety and Health

Carpal tunnel syndrome is a common nerve entrapment disorder. Increasing evidence indicates that occupational factors, especially hand force and repetition, are etiologically related to its development. 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 for use in field studies 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. 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.

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.

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 reporting of symptoms 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 threshed 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

Objective 1. At this time, 144 subjects have been evaluated. Analyses were performed separately for the dominant and non-dominant hands. For the dominant hand, 30 subjects met the criteria for Group 1, 30 for Group 2, and 59 for Group 3. For the non-dominant hand, 27 subjects met the criteria for Group 1, 28 for Group 2, and 64 for Group 3. All thresholds are reported in log microns of peak-to-peak displacement of the vibration stimulator.

The mean differences between digit 2 threshold and digit 5 threshold (2-5DIF) after the wrist flexion period for the dominant hand were 0.01 (SD=0.51) among Group 3 subjects, and 0.67 (SD=1.00) among Group 1 subjects (p=0.002). At a specificity of 80% (2-5DIF>0.29), the sensitivity of this measure for detection of dominant hand carpal tunnel syndrome was 55%. The mean change in 2-5DIF measured before and after the wrist flexion period (DELTA 2-5DIF) was -0.16 (SD=0.58) for Group 3 subjects and 0.40 (SD=1.01) for Group 1 subjects (p=0.009). At a specificity of 80% (DELTA 2-5DIF>0.31), the sensitivity of this measure for detection of dominant hand carpal tunnel syndrome was 41%.

The 2-5DIF after the wrist flexion period for the non-dominant hand were -0.08 (SD=0.44) among Group 3 subjects, and 0.69 (SD=1.23) among Group 1 subjects (p=0.005). At a specificity of 80%, the sensitivity of this measure for detection of dominant hand carpal tunnel syndrome was 60%. The DELTA 2-5DIF was -0.05 (SD=0.37) for Group 3 subjects and 0.50 (SD=0.86) for Group 1 subjects (p=0.004). At a specificity of 80% (DELTA 2-5DIF>0.24), the sensitivity of this measure for detection of dominant hand carpal tunnel syndrome was 52%.

Objective 2. Very few of the Group 1 subjects were willing to undergo even limited repeat nerve conduction velocity testing. No analyses are possible at this time.

Objective 3. Repeat vibrotactile threshold measurements were performed on Group 3 subjects seven months after the initial measurements were made. The mean change in 2-5DIF after wrist flexion over the seven month interval was -0.20 (SD=0.58) for the dominant hand and 0.02 (SD=0.48) for the non-dominant hand. The mean change in DELTA 2-5DIF over the seven month interval was -0.01 (SD=0.86) for the dominant hand and 0.12 (SD=0.70) for the non-dominant hand.

Publications

Letz R, Gerr F: Covariates of Human Peripheral Nerve Function: I. Nerve Conduction Velocity and Amplitude. Neurotoxicology and Teratology, in press, 1993

Gerr F, Letz R: Covariates of Human Peripheral Nerve Function: II. Vibrotactile and Thermal Thresholds. Neurotoxicology and Teratology, in press, 1993

Gerr F, Letz R: Covariates of Human Peripheral Nerve Function: III. Effects of Reported Drinking. Neurotoxicology and Teratology, in press, 1993

Gerr F, Letz R: Vibrotactile Threshold Testing in Occupational Health: A Review of Current Issues and Limitations. Environmental Research 60:145-159, 1993

Gerr F, Letz R, Landrigan PJ: Upper-extremity Musculoskeletal Disorders of Occupational Origin. Annual Review of Public Health 12:543-566, 1991

Gerr F, Letz R, Hershman D, Farraye J, Simpson D: Comparison of Vibrotactile Thresholds with Physical Examination and Electrophysiological Assessment. Muscle and Nerve 14:1059-1066, 1991

Characterization of Posture, Force, and Repetitive Motion

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Importance to Occupational Safety and Health

Cumulative trauma disorders are caused, aggravated, and precipitated by repetitive exertions and movements that workers are routinely required to perform, as well as awkward postures they must assume. Currently, there are no quantitative standards available for protecting workers from

excessive exposure to these hazards. But before dose–response relationships can be established leading to exposure standards for preventing these disorders, practical methods are needed for measuring and characterizing worker exposure to cumulative trauma stress factors. Applications of this theory include assessing exposure to physical stress in a manner analogous to the way sound level meters are used for measuring exposure to acoustic noise.

Objectives

This project is developing efficient analytical techniques for assessing physical stress and strain associated with hand–intensive tasks containing repetitive motion and forceful exertions. It is hypothesized that if the associated power spectrum magnitudes correspond to joint excursion angles and forces at a particular frequency of repetition, then the degree of stress and repetitiveness will be indicated by the spectrum frequency components. Capability for characterizing and reducing stress and strain associated with repetitive motion and exertions are being tested using both industrial tasks simulated in the laboratory and actual tasks performed in the workplace. This investigation further hypothesizes that frequency–weighted filters can be developed, corresponding to human exposure response characteristics as a function of frequency, in order to reduce the data in a single quantity while retaining the relationship between amplitude and frequency.

Methodology

Spectral analysis was investigated as a method for characterizing repetitive wrist motion and postural stress using a simple peg transfer task. Wrist posture was controlled by adjusting the pegboard location and by having subjects reach over an obstruction. Work pace was externally controlled using an auditory signal. Angular wrist flexion/extension and ulnar/radial deviation was recorded using a Penny and Giles strain gage electrogoniometer and sampling the analog signal at a 60 Hz sample rate. Wrist movement data was transformed into the frequency domain for determining the frequency and magnitude of repetitive motion and forceful exertions performed during manual work. Power spectra were computed by stratifying data segments into individual work elements, divided by break points associated with the task. This frequency domain approach was used for averaging elemental data from repetitive cycles.

To test the feasibility of frequency–weighted filters, a psychophysical experiment was conducted for studying the effects of repetition rate (frequency) and repetitive motion (wrist flexion angle) on subjective discomfort. Low force repetitive wrist flexion was studied. A fixture was constructed for limiting wrist flexion limits. Subjects grasped a handle and repetitively flexed and extended at the wrist. Two mechanical stops were adjustable so wrist flexion can be limited between 0° and ±90°. An electronic timer produced a tone indicating the pace.

The full–factorial experiment consisted of five paces and two wrist flexion angles. The timer produced a brief tone indicating to the subject to perform a wrist flexion every 1 s, 2.5 s, 5 s, 10 s, and 20 s. Wrist flexion was limited to 35° and 65°. The experiment was a repeated measures experiment where every subject received all treatments, and subjects was treated as a random effects blocking variable. Each experimental condition was performed for one hour. Five subjects were randomly recruited and paid on an hourly basis. All subjects were right handed females, ranging from 21 yr to 26 yr. Discomfort was measured using the cross–modality matching method. Subjects marked localized discomfort on a 10 cm linear scale, anchored on the left as a no discomfort," and on the right as a very high discomfort." Localized forearm discomfort was assessed every fifteen minutes during a one minute break in the hour long experimental session.

Significant Findings

Peak spectral magnitudes and frequency components corresponded closely with joint displacement amplitudes and repetition rates. Power spectra fundamental frequencies corresponded to the cycle repetition frequency, within the frequency resolution of the spectrum. Spectrum fundamental frequency magnitudes were able to resolve differences in postural changes between different peg board rows. Therefore, this method was not only demonstrated useful for measuring the rate of repetition, but for indicating the magnitude of postural stress for movements at each repetition rate. Spectrum DC component magnitudes were directly related to sustained wrist postures. These components independently measured sustained posture while the AC components measured repetitive movements. Although eliminating the obstruction affected the DC component magnitude, due to the absence of sustained wrist flexion, ulnar/radial deviation DC components and the flexion/extension fundamental frequency magnitude were unaffected.

A linear polynomial regression model for log–transformed discomfort was fitted against the log of wrist flexion angle and the log of frequency. Equal discomfort strata for wrist flexion were determined by solving the regression equation for flexion range at given frequencies for different discomfort levels. This equation was used for specifying attenuation levels needed for high pass filters that weigh repetitive wrist flexion in proportion to the discomfort function. This resulted in a

high–pass filter having a slope of 10 dB/decade. A validation experiment resulted in good agreement between reported discomfort and frequency–weighted wrist movement. This investigation showed that frequency–weighted filters corresponding to discomfort responses associated with exertions and movements at specific frequencies can be developed.

Publications

Radwin RG: An Analytical Method for Characterizing Repetitive Motion and Postural Stress Using Spectral Analysis. Ergonomics 36(4):379–389, 1993

Radwin RG, Lin ML, Yen TY: Exposure Assessment of Biomechanical Stress in Repetitive Manual Work Using Spectral Analysis. Proc of the Human Factors and Ergonomics Society Annual Meeting, 1993

Intracarpal Pressure During Hand Maneuvers

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Importance to Occupational Safety and Health

Carpal tunnel syndrome is the most common entrapment neuropathy in humans and accounts for significant disability, suffering, and cost. There is strong evidence that it is related to occupations involving hand intensive work activity. The long term objective of this line of research is to use intracarpal pressure to specify hand maneuvers that can be safely performed in the workplace, which, if followed, will prevent carpal tunnel syndrome and wrist tendinitis.

Objectives

The specific aims are to (1) determine whether the relationships between CTP and elementary hand maneuvers are consistent between subjects and identify what those relationships are, (2) determine whether the CTP varies significantly within subjects performing typical work–related activities and identify the predictors of that variability, and (3) develop a mathematical model that will predict CTP as a function of elementary hand motions.

Methodology

Fifty normal subjects will be recruited from local newspapers to participate in this laboratory study. A blunt tipped 23–gauge catheter connected to a pressure transducer will be inserted at the wrist into the carpal space. Wrist motion will be tracked with a two–axes electronic goniometer. These outputs and the output of an electronic pinch meter will be sampled at 40 Hz and stored on a microcomputer. The hand maneuvers to be evaluated are: wrist extension/flexion angle and wrist ulnar/radial deviation angle, metacarpophalangeal joint angle, and pinch force. During the first phase, subjects will perform elementary hand maneuvers while data is collected. In the second phase, these results will be used to establish a mathematical relationship between hand maneuvers and ICP. During the third phase, subjects will perform simulated work activities while varying task rate and wrist angle.

Significant Findings

Twenty subjects without carpal tunnel syndrome have been tested to date. As observed by others, this normal population had mean baseline CTP of 7.3 mmHg (s.d. 5.1). The CTP baseline was measured 8 times over a 4 hour period and did not vary: the estimated within–subject variance was 2.2 and the between–subject variance was 22.7.

Subjects were asked to move their wrist and fingers to the one hand position associated with the lowest CTP. The group mean wrist position selected was –3 degrees ulnar deviation (s.d. 8) and 2 degrees of flex ion (s.d. 11). This position is similar to the "optimal – neutral" position suggested by ergonomists and industrial engineers for task design.

Subjects moved their wrists slowly in extension/flexion and ulnar/radial deviation. CTP varied as some parabolic function of wrist position in all subjects. That is, the lowest CTP was near 0 degrees extension/flexion and ulnar/radial deviation and then rose to its highest levels at extremes of extension and flexion, and ulnar and radial deviation. The highest CTPs were recorded at extremes of extension and radial deviation. The highest CTP measured was 220 mmHg. MP angle also modified CTP, but the relationship between MP and CTP remains to be analyzed.

Subjects also pressed with their index finger on a pinch meter to four different load levels (0, 6, 9, and 12 Newtons). This experiment was repeated with the wrist in 10 different position by 15 subjects. Across all subjects and wrist angles, the CTP increased as a function of static load at the fingertip. CTP rose to a high of 80 mmHg in one subject.

Publications

Weiss ND, Gordon L, Bloom T, So Y, Rempel DM: Wrist Position of Lowest Carpal Tunnel Pressure and Implications for Splint Design. J of Hand Surgery, in press, 1994

Weiss N, Bloom T, Gordon L, Rempel D: Wrist Position for Lowest Carpal Tunnel Pressure: A New Method to Measure Intracarpal Pressure as a Function of Wrist Position. Proc of 47th Annual Meeting of American Society for Surgery of the Hand, Phoenix, November 12, 1992

Rempel D, Bloom T, Tal R, Hargens A, Gordon L: A Method of Measuring Intracarpal Pressure and Elementary Hand Maneuvers. Proc of International Scientific Conference on Prevention of Work–Related Musculoskeletal Disorders (PREMUS), Stockholm, 1992

Age & Cumulative Trauma Disorders in Garment Workers

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Importance to Occupational Safety and Health

Cumulative trauma disorders (CTD) constitute a significant occupational health problem in the United States and other industrialized nations. It is generally agreed that CTDs are of multifactorial etiology; work–related and individual characteristics have been implicated by various studies. Specific ergonomic components of manual jobs are thought to be major risk factors for CTD. Although age has been included among the individual risk factors also thought to play a role in CTD incidence, the role that age plays in the etiology of CTDs among workers is relatively unexplored. Furthermore, it is unknown whether there is a potential interactive effect of increasing age and occupational ergonomic factors.

The role of age as a risk factor for occupational injuries or illness is of particular concern in view of the steadily increasing age of the U.S. work force. The rise in average age of workers has especially been noted in older U.S. industries of the manufacturing sector, such as the apparel industry. This study will therefore examine the association between age and CTD prevalence in a garment worker population exposed on the job to varying levels of ergonomic stresses. Improved understanding of risk factors for CTD will be useful in defining intervention strategies for the prevention of this major cause of worker impairment in occupational settings.

Objectives

This study will examine the association between age and CTD prevalence in garment workers, an industrial population with documented levels of ergonomic stresses and a high incidence of CTD. Ergonomic factors will be analyzed and the interaction between age and these factors will be assessed, controlling for other important confounding or effect–modifying variables.

The specific aims of this research are:

1. determine the prevalence of symptoms consistent with cumulative trauma disorders in a garment worker population by a cross–sectional survey.
2. perform observational analyses of individual workers' jobs to characterize ergonomic exposures.
3. develop variables that describe ergonomic risk factors associated with each worker's job, including a quantitative cumulative exposure variable.
4. evaluate potential interactive effects between age and ergonomic risk factors on CTD symptom prevalence.
5. establish baseline data for this cohort of garment workers in preparation for a future follow–up study.

Methodology

This study will be a cross–sectional survey of apparel industry workers. Participants in this study will be workers in a rainwear manufacturing industry

located in the Maryland–Virginia area. Workers of two plants, totalling 566, will be invited to participate voluntarily. Workers of an additional plant from the same company participated in a recent study at a participation rate of 85%.

CTD symptom status, history of CTD diagnosis, age and other individual factors, as well as current ergonomic exposures will be determined concurrently. An on–site job analysis will be performed for each worker using a method of direct observation. An additional measure of ergonomic risk exposure, however, will incorporate retrospective work performance data to create a variable describing each worker's cumulative ergonomic stress experience. The relationships between CTD symptom prevalence, age, and measures of ergonomic exposure will be assessed. This will be done by stratifying data according to levels of ergonomic stressors and analyzing for interactive effects of age and ergonomic factors.

Significant Findings

None to date.

Stochastic Model of Trunk Musculature During Lifting

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Importance to Occupational Safety and Health

Traditionally, biomechanical models of the lumbar spine have assumed that the forces exerted by the trunk muscles in response to external loads are deterministic. That is, given a set of lifting conditions (torque, position, velocity, etc.) the activation of the trunk muscles is precisely determined such that equilibrium exists. However, because of the indeterminate nature of the biomechanical system, variability in the individual muscle forces is not only possible, it is likely. Variability in the individual muscle forces alters the loading patterns on the spine because each muscle has its own vector line of action which has a component in compression, anterior shear and lateral shear. Therefore, by omitting the stochastic nature of trunk muscle activation from the analysis, it is believed that deterministic biomechanical models are not capable of modelling the range of potential spine reaction forces and ultimately are underestimating risk of manual materials handling tasks.

Objectives

The objective of this research project is to develop a stochastic model of the lumbar trunk during lifting. This model will use stochastic principles to predict the activation levels of ten trunk muscles under occupational lifting conditions including varied weights, postures, dynamic components, and asymmetric lifting. This stochastic model will be developed in two phases. In the experimental phase, human subjects will be asked to perform highly controlled simulated lifting motions repeatedly. The electromyographic (EMG) activity of ten trunk muscles will be sampled and will be used to develop a database describing that particular lifting motion. In the modelling phase, this database will be used in a simulation model which will generate potential muscle activities. Multiple runs of the simulation model will generate possible time dependent EMG traces suitable for input into an EMG assisted biomechanical model which will then generate stochastic spine reaction forces.

Methodology

Phase I. EMG data from a sample of college undergraduate and graduate students will be collected as the subjects perform simulated lifting activities. These simulated lifting activities will be described by the following independent variables: sagittal trunk angle (5 and 40 degrees), angular velocity of the trunk (0, 20 and 40 degrees/second), angular acceleration of the trunk (0, 40 and 80 degrees/second/second), trunk extension torque (40 and 80 Nm) and asymmetry of the bending posture (0 and 30 degrees).

To control the levels of the independent variables an experimental apparatus will be used which will place the axis of rotation of a dynamometer in line with the L5/S1 joint of the lumbar spine. The position, velocity, acceleration and torque during trunk extension will be controlled simultaneously by this device. Asymmetry will be controlled by the positioning of the subject in the apparatus.

The dependent variables in this study will be the integrated EMG (IEMG) values for the ten trunk muscles: right and left erector spinae, right and left latissimus dorsi, right and left rectus abdominis, right

and left external obliques and the right and left internal obliques muscles. The EMG signals will be sampled using surface electrodes. In hardware the EMG signals will be filtered (high pass 80, low pass 1000), rectified and a moving average (20ms) will be taken. The EMG data will then be normalized with respect to the trunk angle specific resting and maximum EMG levels.

Phase II. The EMG data collected and processed in Phase I will be used as a data base which will allow us to develop distributions of muscle activities. These distributions will then be used in the simulation model to predict potential EMG vales for each muscle. Our approach during the distribution development phase will be to construct a ten dimensional joint distribution structure. This ten dimensional joint distribution will include 40 marginal distribution parameters (4 distribution parameters for each of the ten trunk muscles) and 45 (10 choose 2) correlation parameters (one for each combination of trunk muscles). Corresponding to a particular lifting condition we will fit a ten–dimensional Johnson distribution to the vector of EMG coactivation responses for the ten muscles. The proposed distribution–fitting technique is a multivariate extension of the techniques for fitting univariate Johnson distributions which possess all of the advantages for statistical modelling and simulation of conventional multivariate Johnson distributions.

The EMG generator model will then use these distributions as a database from which samples will be taken during the simulation. The result will be a time dependent trace of muscle activity for each of the ten trunk muscles. When the simulation model is run multiple times a probabilistic range of potential EMG activity for each muscle will result. The final step in quantifying the internal trunk forces will be to input these generated EMG traces into an EMG–assisted biomechanical model. This will allow one to evaluate the stochastic spinal stresses which would be generated due to the muscle activities predicted by the EMG generator model. It is hoped that this research project will show the pitfalls of using deterministic modelling approach on a system which is inherently probabilistic and give a illustrate a method of modelling risk of low back injury probabilistically.

Significant Findings

None to date.

Occupational Epidemiology of Carpal Tunnel Syndrome

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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. Carpal tunnel syndrome (CTS) is the most commonly reported cumulative trauma disorder. Although CTS has been widely recognized as a clinical syndrome, there are few studies that have examined CTS utilizing rigorous epidemiologic methods. This research examines the magnitude of CTS among selected occupational groups (office workers, court reporters, carpenters, and sprinkler fitters) that have received little epidemiologic attention. The information derived from this research will be useful in assessing the magnitude of CTS and for identifying occupational risk factors for CTS that can be addressed in the development of prevention strategies.

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. Other objectives are to estimate the effects of other factors on CTS occurrence such as psychosocial factors, past medical history, and personal life style factors, and to evaluate diagnosis–related issues of CTS through a comparison of electrodiagnostic findings, objective clinical signs, and symptom reporting.

Methodology

The study design involves two phases: a cross–sectional survey and a nested case–control study of 75 cases and 75 controls selected from the cross–sectional survey population. In the cross–sectional phase, about 4,400 members from three selected unions, representing office workers,

court reporters, carpenters, and sprinkler fitters, received a self-administered questionnaire. These members were 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 in the cross-sectional survey questionnaire and the case-control interview include information on sociodemographic 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, handedness), CTS symptoms and related factors (pain, numbness, tingling and weakness in hands and wrist, use of medical care for symptoms, 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 received 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 included more extensive questions on CTS symptoms, medical history, and occupational work task information. Cases were selected on the basis of their reporting of CTS symptoms, controls were selected from those without CTS symptoms and matched by age, sex, and union.

Significant Findings

The analyses of the cross sectional survey data have been completed. Case-control data collection has also been completed and preliminary analyses are underway and will be available in December 1993.

In the cross-sectional survey, we examined the prevalence of symptoms consistent with carpal tunnel syndrome ("CTS symptoms") among 529 county office workers, 667 active carpenters and sprinkler fitters, and 136 retired trade workers. For office workers, we estimated the effects on CTS symptoms for hours per day using computer keyboards and time involved in repetitive motion activities. For trade workers, we examined hours using power and hand tools, working above shoulder level, and hours involved in repetitive motion activities. We also evaluated the effects of medical conditions, previous injury, and reproductive factors. The adjusted prevalence odds ratios (POR) and 95% confidence intervals (95% CI) for keyboard use and repetitive motion exposures were 1.9 and (1.1, 3.3) and 2.2 and (1.0, 4.9). The effects of hours of keyboard use varied across occupations and were higher among court reporters and data entry staff than among clerks and technical staff. Among trade workers, the POR and 95% CI for repetitive motion activities were 3.2 and (1.6, 6.3). However, power and hand tool use were only modestly associated with CTS symptoms. For all occupations, CTS symptoms decreased with increasing length of employment suggesting healthy-worker selection bias. Several medical conditions and previous injuries were associated with CTS symptoms: rheumatoid arthritis, ganglionic cysts, nerve damage, tendinitis, wrist sprains, and previous hand/wrist injuries. However, these factors were not confounders for the effects of work task exposures on CTS symptoms.

We also examined the relationships between psychosocial factors and hand/wrist symptoms, neck/shoulder pain, and low back pain. The prevalence of experiencing these musculoskeletal conditions in the past month was 20% for all hand/wrist symptoms (pain, tingling and numbness), 59% for one or more of the hand/wrist symptoms, and 56% for neck/shoulder pain, and 52% for low back pain. Our study showed that a stressful psychosocial work environment was associated with increased prevalence of musculoskeletal disorders. Job demand and job satisfaction consistently show an independent effect on all four outcomes. The effect of high job demand appeared to be stronger in females than in males. In addition, the most stressful level of any two psychosocial factors acting together produce a greater combined effect compared to their component effects.

Healthy-worker selection bias and low response rates limit the ability to estimate the effects of workplace exposures. However, these results suggest that, among trade workers, CTS symptoms are higher than what is indicated by studies of workers compensation data. They also suggest that, among office workers, keyboard use and duration of employment were associated with CTS symptoms and that providing a sound physical workplace and a health psychosocial work environment could help to prevent further increase in job-related musculoskeletal conditions.

Publications

Kelsh MA, Ke D, and Morgenstern H: The Importance of Non-occupational Risk Factors in the Assessment of Occupationally-related Carpal Tunnel Syndrome. Abstracts for the Society for Epidemiologic Research Annual Meetings, June, 1993 Keystone, CO. Am J Epidemiol, in press, 1993

Kelsh MA, Morgenstern H, and Ke D: A Cross-sectional Study of Carpal Tunnel Syndrome Symptoms Among Trade and Office Workers. Proc of the Ninth International Symposium, Epidemiology

in Occupational Health, Cincinnati, OH, September, 1992

Effect of Load Asymmetry on Internal Loading of The Trunk

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Importance to Occupational Safety and Health

In industry, carrying and lifting objects asymmetrically is the rule rather than the exception. This situation is hazardous to the musculoskeletal system due to an increase in coactivation of the musculature and an increase of the forces on the spine.

The present study will provide a better understanding of the effect of asymmetrical lifting on mechanical and neuromuscular performance and on the risk of injury to the back.

Objectives

The aim of this study is to quantify the activities of ten trunk muscles by using the surface electromyography (EMG) during maximal and submaximal isometric exertion under pure and combined loading conditions of the trunk. Combined loading is defined as the vectorial sum of moments in the sagittal and transverse planes. These planes are selected based on their prevalence in industrial tasks and low back injuries.

Methodology

To calculate the effect of internal loading, the muscle parameters are calculated from CT-scan images of each individual participant and individual muscle forces are estimated using an EMG-driven model. The compression and shear forces are calculated under suggested conditions. The effects of planar exertion (pure exertion) and combined exertion on the patterns of trunk muscle recruitment and compression and shear forces will be compared.

The primary hypotheses of this study are:

1. The peak EMG activity of trunk muscles will be higher during the maximal combined exertion than during pure maximal exertion.
2. The mean of RMS-EMG of the ten selected trunk muscles will change significantly with the orientation of the net resultant moments of the trunk.
3. The compression and shear forces will be changed significantly by the orientation of the resultant moment.

Significant Findings

None to date.

Occupational Physical Loads and Hip Osteoarthritis

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Start & End Dates: *09/01/93 – 08/31/95*
Funding Level: *$21,310 ($21,310 Cum)*

Importance to Occupational Safety and Health

Osteoarthritis, a common degenerative joint disease, causes substantial morbidity with large attendant economic costs. Establishing an association between this disease and heavy physical loading may give further impetus to efforts aimed at reducing harmful physical exposures in the workplace.

Objectives

Occupational or recreational physical activities which lead to heavy static or dynamic physical loading of the hips may lead to osteoarthritis as a result of cumulative wear or microtrauma. This project will examine the relationship between lifetime

occupational physical exposures and severe osteoarthritis of the hips.

Methodology

In this case–control study, both cases and controls will be recruited from a Health Maintenance Organization (HMO). Cases will be persons aged 50–70 undergoing hip replacement surgery for symptomatic primary (or idiopathic) osteoarthritis. Controls will be HMO members matched by age, sex, geographic catchment area, and length of HMO enrollment. All subjects will complete a self–administered exposure questionnaire which assesses lifetime recreational activities and physical activities at work. Telephone follow–up interviews will be performed with subjects unable to complete the questionnaire. Specific exposures which will be evaluated include lifting, jumping, climbing, whole–body vibration, and work postures. Recreational physical activities and subjects' body weight in different decades of life will be controlled for in analyzing the relationship between occupational physical exposures and hip osteoarthritis.

Significant Findings

None to date.

Prevention of Cumulative Trauma Disorders

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Program Area: *Musculoskeletal Injuries*
Grant Number: *1 R43 OH02907-01*
Start & End Dates: *09/30/91 – 11/30/92*
Funding Level: *$0 ($49,999 Cum)*

Importance to Occupational Safety and Health

Cumulative Trauma Disorders (CTDs) currently account for more than one–half of this country's occupational illnesses, striking an estimated 185,000 U.S. office and factory workers per year. The incidence of these injuries is rising, and currently cost $7 billion a year. Risk factors, including awkward posture, high repetition, forceful actions and vibration are well known. This knowledge however, is based primarily on qualitative data. What has not adequately been determined are the quantitative associations between CTDs and the cited risk factors. The ultimate goal of this research is to establish quantitative relationships between CTDs and work conditions. The end result will be the ability to:

1. Identify work environments which have a high risk of CTDs,
2. Quantify the risk factors thereby allowing a rational, scientific and systematic means of reducing the risk factors, and
3. Verify that ergonomic changes are effective in reducing the risks of CTDs.

The potential for technical innovation is significant because current techniques and technology focus on detecting CTDs after damage is significant. These technologies remain primarily an element of clinical practice and typically rely on advanced CTD symptoms for detection. While patients may already be experiencing significant symptoms of Carpal Tunnel syndrome – numbness and sensory loss in the hand due to compression of the median nerve, atrophy of the thenar eminence, and pain and loss of motor control – nerve conduction tests may remain normal. Some patients have normal nerve conduction results, yet require surgical intervention.

Medical costs can be significantly reduced if CTD risk factors are recognized and corrected early. Therefore, prevention and early detection are of primary importance. This requires the technology used be compatible with both the medical and factory environment. Quantification, prevention, and early detection must be moved out of the research laboratory and medical facility and into the assembly plant, supermarket, and dental office.

Objectives

The first step in developing such quantitative relationships is the attainment of accurate measurements of the relevant risk factors. The GripMaster™ (GM) has the potential to be an ergonomic tool capable of measuring these parameters. This Phase I project was designed to validate the GM's measurement of wrist motion and finger and hand force, and to develop a strategy for advancing this technology to the point where it is accurate and viable in a field/factory environment.

Methodology

Two classes of experiments were performed; laboratory and field. The laboratory testing focused directly on comparing the GM to other measurement techniques: hand dynamometers and EMG for force measurement; video analysis and manual goniometry for angle measurement. The field testing was a pilot

study designed to verify consistent operation of the GM between the laboratory and the field environment and to identify operational parameters influencing the functional capability of the GM.

Laboratory experiments were conducted at University of Massachusetts, Amherst (UMASS). Three static grip force experiments were conducted. The GM's force measurements were compared to a hand dynamometer and EMG measurement techniques in static hook, power, and pinch grips. The GM's measurement of static wrist postures were also compared to video analysis techniques in the laboratory experiments. The reliability of the GM's force sensors was also tested.

The field testing was conducted at a lock manufacturing facility over a period of two days. Data analysis of the laboratory and field experiments were conducted at both UMASS and EXOS, Inc.

Significant Findings

This Phase I project was designed to validate the measurements of wrist motion and finger and hand force provided by the GripMaster™ (GM) and to develop a strategy for advancing this technology to the point where it is accurate and viable in a field/factory environment. The GM tested in this study showed high correlation to more established techniques when the contact area was constant and sensors were new. Angle measurements were shown to be as accurate as current clinical techniques. It was demonstrated that it is feasible to use a tool like the GM in the field environment, but operational parameters identified in the field provide additional requirements for further development of this technology.

Occupational Cancer Surveillance: New Approaches

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Start & End Dates: *09/28/84 – 09/29/94*
Funding Level: *$0 ($1,233,788 Cum)*

Importance to Occupational Safety and Health

The Occupational Cancer Incidence Surveillance System (OCISS) developed by this study will contribute to reduction of morbidity and mortality due to occupational risk factors for eleven types of cancer. It has developed both methodologic and substantive leads that contribute to prevention programs as well as to future 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. OCISS data have contributed to the methodology of occupational epidemiology, having demonstrated that occupational information derived from death certificates provides incomplete information about occupational cancer risk. Our studies also have demonstrated that direct information about cigarette smoking histories is essential to occupational cancer studies. Data from OCISS and related studies will ultimately be utilized to develop cancer prevention programs in the workplace.

Objectives

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 tobacco.
4. To develop new methodologic approaches for occupational epidemiology.

Methodology

Detailed work histories, tobacco use histories, health history, and demographics have been obtained by telephone interview. Cancer cases were selected from a population–based registry; population referents were selected by random digit dialing. Eleven cancer sites are included in this study. A total of 16,888 cancer patients were interviewed, including 6,349 with lung cancer, 2,443 with urinary bladder cancer, 3,211 with colon cancer, 1,428 with cancer of the rectum, 1,111 with cancer of the esophagus, 795 with stomach cancer, 540 with liver cancer, 570 with cutaneous melanoma, 178 with cancer of the salivary glands, and 127 with eye cancers. There were 3,913 population referents interviewed.

Significant Findings

Analysis of usual occupation and industry among lung cancer cases revealed excess risks for farmers, excavating and mining workers, driver sales, furnace workers, armed services personnel, truck drivers, mechanics, and painters; excess risks also were seen in the mining, farming, and primary ferrous metals manufacturing industries. Five of these occupations have exposure to diesel exhaust. Assessment of these risks separately for black and white men revealed that the risk among mechanics was restricted to black males and that the risk among armed services personnel was considerably higher in black males than among white males.

Analysis of urinary bladder cancer revealed excess risk among armed services personnel for white males and among automobile mechanics for black males. These data also reveal a higher attributable risk for cigarette smoking among bladder cancer than previously observed – 51%. Industries with elevated risk among bladder cancer patients included wood manufacturing, drug manufacturing, hardware sales, and other transportation manufacturing.

An important contribution of this project to the discipline of occupational cancer epidemiology is the clear demonstration that men and women and blacks and whites have different workplace cancer risks, even when employed in the same occupations or industries. Our analyses of cancer risks among black and white men show that Odds Ratios are different for these two groups in nearly every occupation and

industry. This is an important finding, indicating not only that blacks must be included in occupational cancer epidemiology studies, but also that they must be evaluated separately from white men.

A comprehensive analysis of occupational risks among women for each of the eleven cancer sites was conducted, with summary results presented to the International Conference on Women's Health: Occupation and Cancer in Baltimore on November 1, 1993. This conference was the first ever to focus upon occupational cancer risks among women and it was co-sponsored by the National Institute for Occupational Safety and Health, the National Cancer Institute, the National Institute of Environmental Health Sciences, and the NIH Office of Research on Women's Health. The OCISS results provided extensive information about specific methodologic issues that must be addressed in investigations of cancer risk in the workplace among women and provided new leads about several occupations and industries and their association with specific cancers. Methodologic issues include: (1) a large proportion of women in the age range of highest incidence of the cancers studied had a usual occupation of housewife (ranging from 54% among women diagnosed with cancer of the salivary gland to 76% for women diagnosed with eye tumors and 63% for population controls); (2) the small number of categories of either occupations or industries with even 10 cases or controls (there were 10 or more cases in 1 to 14 occupation groups and 0 to 12 industry groups across the eleven cancer sites); and (3) it is necessary to assess occupational risk among women ever employed in specific occupations or industries, as well as usual occupation and industry, since among those with housewife as usual occupation, 80% held some other job). These limitations are particularly striking, since OCISS includes much larger numbers of women than most occupational cancer studies—there are nearly 6000 cancer cases and 2000 controls who are women.

Even with these limitations, new leads regarding the association between specific occupations or industries and specific cancer sites were obtained. These include a four-fold increase among women in the computer manufacturing industry among those diagnosed with bladder cancer, a two-fold excess of women employed in restaurants among those diagnosed with cancer of the esophagus, a three-fold excess of women employed in hairdressing shops among those diagnosed with cancers of the salivary gland, an eight-fold elevation of women in the beverage manufacturing industry among those diagnosed with bladder cancer, a three-fold excess of women employed in food stores who were diagnosed with stomach cancer, and four-fold increases among both women employed in bus and truck services and in military service among those diagnosed with eye cancers. Although not statistically significant, there was a large excess of women ever employed as tool and die workers who were diagnosed with cancers of the salivary gland (OR=8.5).

Publications

Swanson GM, Lin C-S, Burns PB: Diversity in the Association Between Occupation and Lung Cancer Among Black and White Men. Cancer Epidemiology, Biomarkers, and Prevention 2(4):313-320, 1993

Burns PB, Swanson GM: Risk of Urinary Bladder Cancer Among Blacks and Whites: The Role of Cigarette Use and Occupation. Cancer Causes and Control 2:317-379, 1991

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. Am J Ind Med 19:655-671, 1991

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 J 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(12):1532-1534, 1987

Swanson GM, Schwartz AG, Brown KL: Population-Based Occupational Cancer Incidence Surveillance - Utilization of the Telephone Interview. J Occup Med 27(6):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 J Public Health 74(5):464-467, 1984

Biological Monitoring/Risk Assessment In An Exposed Cohort

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Importance to Occupational Safety and Health

Thousands of workers worldwide are at increased risk of bladder cancer because of previous exposure to aromatic a mines. 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 this 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 primary objectives of this research are to continue screening studies in a cohort of workers occupationally exposed to benzidine to both develop a bladder cancer screening approach as well as to reduce the number of deaths and serious morbidity associated with bladder cancer in this cohort. The ultimate aim is to devise a strategy that will detect persons likely to develop dangerous, invasive disease early enough to alter potentially unfavorable outcomes and release those at little elevated risk. The detection window during which this can be achieved with conventional screening techniques is very narrow, but can be widened with new tests based upon detecting the emerging malignant phenotype rather than waiting for frank cancer. The long–term goals are to develop a strategy based upon a combination of biochemical intermediate markers and clinical signs and symptoms, combined with assessments of various exposures to (1) assess the bladder cancer risk faced by an individual and (2) more effectively manage such individuals to minimize their risk.

Methodology

We propose to continue to screen and monitor a cohort of approximately 2,000 Chinese workers exposed to benzidine to identify confirmed and presumptive cases of bladder cancer and conduct a risk factor analysis. This large worker population is located in five cities — Shanghai, Jilin, Tianjin, Chongqing, and Henan — in the People's Republic of China.

Significant Findings

In a pilot study and the 2–year bladder cancer screening program which preceded the present study, we detected bladder cancer in its earliest stages prior to detection by conventional cytologic criteria using a biomarker profile consisting of G–actin, a marker for early differentiation changes, the p300 tumor related antigen detected with M344 monoclonal antibody, and abnormal DNA ploidy detected by the presence of cells with >5C DNA. We have screened 1686 exposed male workers and 388 unexposed male controls matched for age and smoking history. Preliminary statistical analysis of the results from workers in two of the cities using the previously defined panel of biomarkers using both χ^2 and Logistic Regression, identified highly significant correlations ($p < 0.05$ to 0.0001) with duration of benzidine exposure, pack–years smoked, and urinary stasis associated with benign prostatic hypertrophy, all of which are also risk factors for bladder cancer. The currently employed weighted exposure index and hematuria did not correlate with the biomarkers. The current study is designed to assess the bladder cancer risk of exposed individuals and validate using a panel of biomarkers for risk assessment. The original screening of this cohort has yielded three subject groups. From screening the worker groups in

Shanghai and Chongqing, we estimate the numbers in each group (totals of exposed and controls) to be: Group 1 – negative for any biomarkers (about 1500 subjects); Group 2 – positive for one marker (about 400 subjects); and Group 3 – positive for two or more markers (about 150 subjects). We plan to screen Group 1 every 3 years, Group 2 every year (or five times during the study), and Group 3, the highest risk group, every 6 months (or 10 times during the study). Group 3 will include urological followup, and screening in Groups 2 and 3 will include additional, more specific markers to further stratify risk within the groups and to investigate the relationships among such markers in the carcinogenic process.

Publications

Bi WF, Rao JY, Hemstreet GP, Yin S, Asal NR, Zang M, Min KW, Ma Z, Fang P, Lee E, Li G, Hurst RE, Wu W, Bonner RB, Wang Y, Fradet Y: Field Molecular Epidemiology: Feasibility of Monitoring For The Malignant Bladder Cell Phenotype In A Benzidine–exposed Occupational Cohort. J Occup Med 35:20–27, 1993

Rao JY, Hemstreet GP, Hurst RE, Bonner RB, Jones PL, Min KW, Fradet Y: Alterations In Phenotypic Biochemical Markers In Bladder Epithelium During Tumorigenesis. Proc Nat Acad Sci, USA 90:8287–8291, 1993

Bonner RB, Hemstreet GP, Fradet Y, Rao JY, Min KW, Hurst RE: Bladder Cancer Risk Assessment With Quantitative Fluorescence Image Analysis Of Tumor Markers In Exfoliated Bladder Cells. Cancer 72(8):2461–2469, 1993

Case Control Study of Cancer in Synthetic Rubber Workers

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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 Internal Agency for Research on Cancer considered the chemical to be "possibly carcinogenic."

In the 1950s and 1960s, toxicologists tested some for 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 emphasizes human effects from exposure to butadiene based on industrial monitoring measures.

Objectives

The goals of this research are to examine the risk of mortality from lympho–hematopoietic, 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) 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. (3) 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.

Significant Findings

The study showed that even when using different methodologies such as choosing different types of controls, the risk of leukemia among workers in this industry remains high. Analysis of the case–control sets matched for duration worked have compared cases with gastrointestinal cancers and controls above and below the median butadiene exposure to subjects with no exposure in an exact analysis. Although some of the odds ratios are high for butadiene and styrene associated with esophagal cancers and there is a suggestive trend for increasing odds ratios with increasing butadiene exposure for colorectal cancers, none of the results are significant. These data need to be reexamined using measurement data and controls which are not matched for duration of exposure.

Hospital records were sought for all cases of lymphohematopoietic and gastrointestinal cancers included in the study. Of those with a diagnosis of leukemia, a higher proportion were acute lymphocytic leukemia than would be expected based on SEER data. Unusual observations were also made when reviewing hospital records of patients with gastrointestinal cancers. Two of the soft tissue sarcomas are angiosarcomas (one of the liver, the other of the femur). According to SEER data, this cell type and the fibrosarcomas are occurring at a frequency much higher than expected.

The inclusion of short–term workers (those with less than one year of employment) in the cohort analysis has increased the all cause mortality but remarkably did not increase the SMRs for cancer or circulatory diseases. For cancers of interest in the current research, the long–term workers have higher risks than short–term workers. This might suggest that those exposed in the industry the longest are at highest risk of cancer. The data indicate that inclusion of these short–term workers does not add to the risk of lymphohematopoietic and gastrointestinal cancers.

Biologic importance of the work: In repeated analyses using different control groups, the risk of lymphohematopoietic cancers was increased in workers who had increased exposure to butadiene. This has important implications with regard to the present consideration of a safe standard to set for anyone exposed to butadiene.

Methodologic importance of the work: Choosing new leukemia controls who were not matched for duration of employment resulted in a slightly lower odds ratio for butadiene. However, when duration was added to the model, the odds ratio for butadiene was higher than the original odds ratio using duration matched controls. The model with both butadiene and styrene is significant at p=.02. This may mean that the dose in a fixed time period is more important than total cumulative dose. This is very important since most occupational studies have used duration worked as the marker of "dose."

The application of measurement data to describe dose in a population at risk is complicated and needs to be approached with caution. The job titles abstracted from the personnel records and the jobs on the samples may not be compatible. Not all job titles are sampled and the reason for sampling is not always clear. Samples used for a purpose other than that for which they were collected may have other short–comings which are not immediately obvious.

Publications

Matanoski GM, Francis M, Correa–Villasenor A, Elliott EA, Santos–Burgoa C, Schwartz L: Cancer Epidemiology Among Styrene Butadiene Rubber Workers. Accepted for publication. International Symposium on Health Hazards of Butadiene and Styrene, Espoo, Finland, April 1993.

Santos–Burgoa C, Matanoski GM, Zeger S, Schwartz L: Lymhohematopoietic Cancer in Styrene–Butadiene Polymerization Workers. Am J Epidmiol 136:843–854, 1992

Improved Magnetic Field Exposure Assessment

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Importance to Occupational Safety and Health

The accurate assessment of magnetic field exposure is essential to the epidemiologic evaluation of the hypothesis that these fields contribute to

increased cancer or reproductive risk. This investigation is evaluating methods for making appropriate exposure assignments to worker subjects in epidemiologic studies, and for choosing efficient measurement strategies.

Objectives

The objectives of the project are to improve the characterization of magnetic field exposures and their variability in the workplace and to evaluate alternative measurement strategies. Central to these objectives is the accurate assessment of the degree of exposure variability within given work locations (which is thought to be greater than for airborne hazards), and over time for given subjects.

Methodology

Exposure data from both a personal dosimeter and a hand–held "spot" magnetic field meter were available for these investigations. The data were collected at a large automobile transmission plant in the midwestern U.S. The dosimeters were worn by a representative group of 81 workers for approximately 200 minutes each, recording a measurement every 4 seconds. These data were reduced to series of 1 minute averages for further analysis of between–worker and temporal variability. Since there is little biological guidance on possible disease mechanisms, six different exposure metrics were computed for each worker, and these were compared with one another.

The spot meter was also used to take multiple measurements at each of the work locations of the production and assembly workers among those wearing the dosimeter. Estimates were made of time spent at each of these locations, so that 'built–up' average exposure estimates could be made; these were then compared to average exposures derived from the dosimeter. Source identification and exposure falloff with distance were also evaluated with this spot meter.

Significant Findings

Background exposure at this heavy industrial plant was surprisingly low, less than 0.2 milliGauss (mG). This compares with a 25th percentile for home exposures of 0.4 mG in a large survey of electric utility workers who wore the same dosimeter at work and at home. The median of the workers' average exposures was also not particularly high, namely 1.3 mG, though 25 percent of the measured workers had exposures above 2.5 mG. Moment to moment exposure variability was very large, with some workers' 1 minute averages varying over four orders of magnitude. The highest average exposure found was 46 mG.

The "built–up" average exposures, which were calculated from spot measurements and time estimates at each locations, were compared to average magnetic field exposure as derived from the dosimeter records; correlations were found to be very high between the two averages.

Little information was available prior to this survey about principal magnetic field sources in the metalworking industry. Our initial hypothesis was that electric motors would predominate, but other unexpected strong sources were found. Most important were demagnetizers, which in some cases strongly affected worker exposures as far away as 12 meters. These devices are used to remove permanent magnetism which has been induced in some parts by grinding operations.

With very limited biological guidance on how magnetic fields might contribute to cancer promotion, six different exposure metrics have been computed for each worker, reflecting several possible mechanisms of harm. These metrics included measures of central tendency, time spent above possible thresholds, and indicators of exposure profile irregularity. This last characteristic has recently been suggested to have biological significance in laboratory experiments. Correlations between some of these indices are moderately high, but not high enough to assume that exposure assignments for epidemiology would yield the same results with each of them.

Environmental Exposures and Risk Digestive Cancers

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Importance to Occupational Safety and Health

The applicants have recently found excesses of several digestive cancers of *a priori* interest in a large cohort of automobile workers with exposure to metal working fluids. Since the previous application

we have completed an exposure–response analysis based on internal comparisons in the full cohort of autoworkers. Based on results of Poisson regression models, statistically significant relative risks of up to three fold were found between esophagus cancer and increasing levels of exposure of machining fluids used in the course of grinding operations. Evidence of weaker associations, between 1.5 and 2.0, were observed between grinding and stomach and pancreatic cancer. Strong evidence was also observed for associations between straight machining fluids and rectal and larynx cancer.

NIOSH has estimated that 1.2 million workers in the U.S. engaged in metal grinding or machining operations are exposed to these fluids, while over 6 million workers are more generally exposed to the various components of the fluids. Better specification of the causal agents is necessary for an assessment of risk associated with metal working fluids in use today.

Objectives

This revised proposal requests funds to further examine the elevated risks for cancer of the esophagus, stomach, pancreas, colon and rectum in this cohort of autoworkers with exposure to machining fluids. A series of nested case–control analyses will be conducted. The objective of the study is to identify the specific agent(s) in the machining fluids which are causing the elevated cancers in this cohort.

Methodology

Conditional logistic regression models will be used to provide estimates of adjusted Odds Ratios for the major fluids types as well as specific components of the fluids such as sulfur, chlorine, selected metals, nitrosamines and biocides. Semi–quantitative estimates of exposure to sulfur and polycyclic aromatic hydrocarbones (PAH) will also be developed in the proposed study and included in the exposure–response models.

Significant Findings

None to date.

New Method for Occupational Cancer Surveillance

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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. The assays 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 sero prevalence 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

Results on cancer patients and controls indicate this assay to be highly sensitive (detecting sub–nanogram quantities of oncoprotein), specific and reproducible. Results in the serum of lung cancer patients appear consistent with studies of tumor tissue. In particular, a significant proportion of lung cancer patients (33–45%) exhibit elevation of the p21 ras oncogene protein compared to low rates (<5%) in normal, health controls; in addition, a small percentage of lung cancer patients (<5%) exhibit point mutated forms of p21 in their serum. Also, a significant proportion of colon cancer patients (30–35%) exhibit elevation of the p21 ras oncogene protein, as do a significant proportion of colonic polyp patients (15–20%); the highest proportions of serum positive cases were among those with large polyp (30%) and those with carcinoma *in situ* (65%), suggesting that serum p21 may be a useful early marker of oncogenic change. Furthermore, analysis of results from occupationally exposed cohorts are consistent in that a significant proportion of asbestos–exposed workers who developed respiratory malignancies (45%) demonstrated elevated serum expression of p21, and this elevation was significant on the average of 16 months prior to the time of clinical diagnosis of disease. This confirms that serum p21 can be a useful early marker of preclinical carcinogenic pulmonary response in persons with respiratory exposure to carcinogens. Analysis of the results for serum growth factors, such as PDGF and TGF–B, in this cohort and other asbestos–exposed groups further suggest that elevated serum growth factors correlate with severity and progression of non–malignant respiratory disease, in particular pneumoconiosis. Application of this approach to environmentally exposed cohorts in Eastern Europe show that populations exposed to high ambient levels of carcinogens have twice the rate of elevated serum p21 protein expression as unexposed controls (10% in exposed vs 5% in controls). Analysis for point mutated forms of p21 (Asp 13) in vinyl chloride exposed workers indicate that individuals who develop hemangiosarcomas have detectable protein in their serum and tumor tissue (with confirming mutations in tumor DNA), and that a high proportion (50%) of individuals with long–term, high exposure also express the protein in their serum. Studies of effective, oncogene–specific chemo prophylactic intervention development for such cohorts are underway. Finally, the analytical approach is being applied to the detection of serum tumor suppressor gene proteins, such as p53, in similarly exposed cohorts.

Publications

Brandt–Rauf PW, Pincus MR, Carney WP: The C–erbB–2 Protein in Oncogenesis: Molecular Structure to Molecular Epidemiology. Critical Reviews in Oncogenesis, in press, 1993

Brandt–Rauf PW, Luo JC, Carney WP, Smith S, DeVivo I, Milling C, Hemminki K, Koskinen H, Vainio H, Neugut AI: The Detection of Increased Amounts of the Extracellular Domain of the C–erbB–2 Oncoprotein in Serum During Pulmonary Carcinogenesis in Humans. International Journal of Cancer, in press, 1993

Luo JC, Zehab R, Antilla S, Ridanpaa M, Husgafvel–Pursiainen K, Vainio H, Carney W, DeVivo I, Milling C, Brandt–Rauf PW: The Detection of Serum p53 Protein in Lung Cancer Patients. Journal of Occupational Medicine, in press, 1993

Breuer B, DeVivo I, Luo JC, Smith S, Pincus MR, Tatum AH, Daucher J, Minick CR, Miller DG, Novak EJ, Cody HS, Niman H, Carney WP, Brandt–Rauf PW: ErbB–2 and Myc Oncoproteins in Sera and Tumors of Breast Cancer Patients. Cancer Epidemiology, Biomarkers and Prevention, in press, 1993

Vineis P, Brandt–Rauf PW: Mechanisms of Carcinogenesis: Chemical Exposure and Molecular Changes. European Journal of Cancer 29A:1344–1347, 1993

Breuer B, Luo JC, DeVivo I, Pincus M, Tatum AH, Daucher J, Minick R, Osborne M, Miller D, Nowak E, Cody H, Carney WP, Brandt–Rauf PW: Detection of Elevated C–erbB–2 Oncoprotein in the Serum and Tissue in Breast Cancer. Medical Science Research 21:383–384, 1993

Luo JC, Yu MW, Chen CJ, Santella RM, Carney WP, Brandt–Rauf PW: Serum C–erbB–2 Oncopeptide in Hepatocellular Carcinogenesis. Medical Science Research 21:305–307, 1993

DeVivo I, Breuer B, Smith S, Milling C, Pincus M, Tatum AH, Daucher J, Niman H, Minick R, Osborne M, Miller D, Nowak E, Cody H,

Brandt–Rauf PW: Detection of Serum C–myc Oncoprotein in cancer Patients by Immunoblot. Medical Science Research 21:345–347, 1993

Brandt–Rauf PW, Smith S, Hemminki K, Koskinen H, Vainio H, Niman H, Ford J: Serum Oncoproteins and Growth Factors in Asbestosis and Silicosis Patients. International Journal of Cancer 50:881–885, 1992

Perera FP, Hemminki K, Gryzbowska E, Motykiewicz G, Santella RM, Young TL, Dickey C, Brandt–Rauf PW, De Vivo I, Blaner W, Tsai WY, Chorazy M: Molecular and Genetic Damage in Humans from Environmental Pollution in Poland. Nature 360:256–258, 1992

Brandt–Rauf PW: Oncogenes and Oncoproteins in Occupational Carcinogenesis. Scandinavian Journal of Work, Environment and Health 18:27–30, 1992

Brandt–Rauf PW: The Molecular Epidemiology of Oncoproteins. Scandinavian Journal of Work, Environment and Health 18:46–49, 1992

Ford J, Smith S, Luo JC, Friedman–Jimenez G, Markowitz S, Garibaldi K, Niman H, Brandt–Rauf PW: Serum Growth Factors and Oncoproteins in Firefighters. Occupational Medicine 42:39–42, 1992

Perera FP, Santella R, Brandt–Rauf PW, Kahn S, Jiang W, Mayer J: Molecular Epidemiology of Lung Cancer. In: Origins of Human Cancers: A Comprehensive Review, (ed. H Hiatt), Cold Spring Harbor Laboratory, Cold Spring Harbor, pp. 219–236, 1991

Perera FP, Santella RM, Brandt–Rauf PW, Kahn S, Jiang W, Tang D, Mayer J: The Role of Molecular Epidemiology in Cancer Prevention. In: Xenobiotics and Cancer: Implications of Chemical Carcinogenesis and Cancer Chemotherapy, (eds. L Ernster, H Esumi, Y Fujii, HV Gelboin, R Kato, T Sugimura), Japan Scientific Societies Press, Tokyo, pp. 339–350, 1991

Brandt–Rauf PW: Advances in Cancer Biomarkers as Applied to Chemical Exposures: The ras Oncogene and p21 Protein and Pulmonary Carcinogenesis. Journal of Occupational Medicine 33:951–955, 1991

Luo JC, Neugut AI, Nieves J, Benson M, Niman H, Brandt–Rauf PW: Int–1 Related Proteins in Serum of Prostate Cancer Patients and Controls. Medical Science Research 19:453–454, 1991

Brandt–Rauf PW: Oncogene Proteins as Biomarkers in the Molecular Epidemiology of Occupational Carcinogenesis: The Example of the ras Oncogene Encoded p21 Protein. International Archives of Occupational and Environmental Health 63:1–8, 1991

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 90:247–254, 1991

Ford J, Smith S, Markowitz S, Brandt–Rauf PW: Increased Levels of TGF–B in Serum of Firefighters. American Review of Respiratory Disease 143:A103,1991 (Abstract)

Brandt–Rauf PW: Advances in Cancer Biomarkers as Applied to Chemical Exposures. Journal of Occupational Medicine 33:537, 1991 (Abstract)

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 14:639–645, 1990

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. 164–180, 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: Serum Screening for Oncogene Proteins in Occupationally Exposed Workers. Journal of Cancer Research and Clinical Oncology 116:982, 1990 (Abstract)

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

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Importance to Occupational Safety and Health

Humans are exposed to a wide variety of carcinogenic compounds, many of which are unidentified. Individuals within the same occupational environment receive different levels of exposure to chemicals depending on their specific tasks and personal habits. Even individuals receiving the same dose of carcinogen exposure will differ in their sensitivity to the chemical due to differences in metabolism and excretion based on genetics, sex, age, and nutritional and health status. The work supported by this grant seeks to develop a method for determining the actual dose of carcinogen received by individuals in order to set appropriate limits for such exposures and to evaluate safety measures taken to reduce exposures.

Objectives

The major goal of this research is to determine if the measurement of DNA-carcinogen adducts in circulating white blood cells (WBC) 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

Inbred mice are used as an animal model of human exposure to the arylamine carcinogen 2-aminofluorene (2-AF). The animal model allows for controlled exposure to known doses of a specific carcinogen for selected time periods. In addition, the animal model permits access to internal target tissues of the carcinogen. Thus, dose-response measurements comparing carcinogen exposure to DNA-carcinogen adduct production can be made in the bio-marker and in the target tissue.

Acute exposure to 2-AF is achieved by intraperitoneal injection. Subchronic exposure is by addition of 2-AF to the drinking water. DNA is isolated from WBC, liver, and bladder of control and carcinogen treated mice. DNA-carcinogen adducts are detected and quantitated by ^{32}P-postlabeling of nucleotides obtained by enzymatic hydrolysis of DNA followed by HPLC analysis of adducted nucleotides.

The ability of white blood cells to activate carcinogens is examined by isolating mouse white blood cells and incubating them with carcinogen for 12 to 24 hours under standard cell culture conditions. The cells are harvested, DNA prepared, and adducts analyzed by ^{32}P-postlabeling followed by HPLC and scintillation counting.

Significant Findings

In mice, the formation of 2-aminofluorene-DNA adducts in the target tissues liver and bladder is dependent on a number of factors that can modify the metabolic activation of 2-aminofluorene. Among these are age at time of exposure, sex, and acetylator status. Studies of these variables have indicated that acetylator status is of major significance in hepatic DNA adduction, while age at time of exposure is

particularly important in bladder adduct formation in male mice. Sex is a significant determinant of which tissue will be the major target of DNA damage (liver in females and bladder in males). In order to simplify initial comparisons between target tissues and WBC, we have examined C57BL/6J (rapid acetylators) male mice at 7 weeks of age.

The formation and disappearance of WBC DNA adducts for 24 hr after exposure to 2–aminofluorene was measured and compared with liver and urinary bladder DNA adducts. In general, adduction of DNA by 2–AF metabolites appeared similar in the three tissues. The highest level of 2–AF–DNA adducts were observed at 3 hr and decreased with time over the period studied. The decline in WBC adducts during the 24 hr period was parallel to the decline in liver adduct levels; WBC adducts were between 11% and 14% of liver adduct levels for the period. A similar relationship between WBC and bladder adducts was only observed for the first 12 hr, during which WBC adducts were about 5% of bladder adduct levels.

Seven day continuous exposure experiments demonstrated a clear dose response between the amount of 2–AF consumed and DNA adduct formation in both leukocytes and the target tissues. Increasing the concentration of 2–AF in the drinking water produced an almost linear increase in DNA adducts in all 3 tissues examined.

The findings indicate that WBC are potentially useful as exposure indicators both for acute and chronic exposures to the arylamine carcinogen 2–AF and that WBC are worthy of further investigation as biological monitors of DNA damage in internal target tissues. The parallel decline in adduct levels in WBC and liver after acute exposure and the similar dose–response curves for WBC, liver, and bladder DNA adduct formation during continuous exposure indicate WBC may be very useful in determining individual carcinogen exposure levels.

Cultured mononuclear leukocytes (MNL) demonstrated the ability to activate 2–AF and form DNA adducts. The extent of adduct formation was related to the genetically determined ability of MNL to activate 2–AF. Incubation of isolated MNL with carcinogen followed by DNA–carcinogen adduct measurement may give an indication of individual susceptibility to DNA damage.

Publications

Levy GN, Chung JG, Weber WW: 2–Aminofluorene Metabolism and DNA Adduct Formation by Mononuclear Leukocytes from Rapid and Slow Acetylator Mouse Strains. Carcinogenesis 15, in press, 1994

Chung JG, Levy GN, Weber WW: The Distribution of 2–Aminofluorene and *p*–Aminobenzoic Acid N–Acetyltransferase Activity in Tissues of C57BL/6J Rapid and B6.A–*Nat*^{s} Slow Acetylator Congenic Mice. Drug Metab Dispo 21, in press, 1993

Levy GN: Ciculating Leukocytes as Indicators of Arylamine Carcinogen Exposure. Fund Appl Toxicol 21:23–30, 1993

Levy GN, Martell KJ, DeLeon JH, Weber WW: Metabolic, Molecular Genetic, and Toxicologic Aspects of the Acetylation Polymorphism in Inbred Mice. Pharmacogenetics, in press, 1992

Levy GN: Circulating Leukocytes as Indicators of Arylamine Carcinogen Exposure. The Toxicologist 12:189, 1992 (Abstract)

Levy GN, Weber WW: 2–Aminofluorene–DNA Adducts in Mouse Urinary Bladder: Effect of Age, Sex, and Acetylator Phenotype. Carcinogenesis 13:159–164, 1992

Susceptibility to Genetic Damage from Butadiene

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Importance to Occupational Safety and Health

In recent years there has been a growing interest in the application of biomarkers in cancer epidemiology. The current research is being conducted with an emphasis on genotoxic and mutagenic markers and the genetic modifiers of sister chromatid exchange induction. Such modifications will likely have relevance for the prevention of occupationally–induced cancers.

Objectives

The objectives of this research are to determine the extent of genotoxicity attributable to 1,3–butadiene exposure in humans in the workplace and to test whether chromosomal sensitivity to diepoxybutane predicts individual susceptibility to genotoxic effects of butadiene exposure.

Methodology

Butadiene workers involved in monomer and polymer production were studied. Exposure was assessed by questionnaire, workplace walk–throughs and personal and area monitoring. Butadiene–exposed workers contributed a blood sample and chromosomal endpoints were analyzed. Individual sensitivity to the cytogenetic effects of diepoxybutane added *in vitro* was assessed. Analysis was completed to determine if individual cytogenetic sensitivity to diepoxybutane predicts the baseline level of chromosome damage induced by butadiene exposure. In this way, susceptibility to the chromosomal effects of butadiene was examined by looking at chromosomal sensitivity to the butadiene metabolite, diepoxybutane.

Significant Findings

The field portion of the study has been completed. Exposure to butadiene has been assessed with 8–hour time wait of average personal sampling as well as urine collection and metabolite determination. Significant data has been collected by questionnaire and blood has also been collected. Early analysis of the data reveals baseline cytogenetic changes in the exposed group to be unrelated to time–weighted average measurements of exposure. Urine was collected and there is no relationship between induced cytogenetic damage and urinary measures of exposure to butadiene. However, examination of high SCE frequency cells reveals that there is some relationship between length and the trade and high frequency SCE cells present in workers. Also, one individual who had previously been noted to have a very high hprt mutant fraction was also sensitive to diepoxybutane *in vitro*.

Thus, our work indicates that acute exposure to 1,3–butadiene was not associated with induction of chromosomal abnormalities. However, tenure in the trade was associated with production of high SCE frequency cells. Companion studies of molecular epidemiology are being carried out using these same techniques. These studies have shown that genetic damage, induced by exposure to radiation results in persistent genetic damage measured as sematic mutations. Further, we've noted that constitutional heterozygosity for the ataxia–telangiectasia gene results in heterogeneity in the clastogenic response to x–rays in lymphocytes from these individuals. In addition, molecular determination of the heterozygosity in glutathione transferase class μ does not modify venodilatory potency of nitroglycerin in human veins.

Publications

Wiencke JK, Kelsey KT: Susceptibility To Chromosomal Damage Induction by Metabolites of 1,3–Butadiene and Its Relationship To "Spontaneous" Sister Chromatid Exchange Frequencies in Human Lymphocytes, IARC Monograph, (ed. M Sorsa), in press, 1993

Wiencke JK, Kelsey KT: Susceptibility To Induction of Chromosomal Damage by Metabolites of 1,3–Butadiene and Its Relationship To "Spontaneous" Sister Chromatid Exchange Frequencies in Human Lymphocytes, IARC Scientific Publications No. 127, (eds. M Sorsa, K Pelionen, H Vainio, K Hemminki), Lyon, International Agency for Research on Cancer, 1993

Kelsey KT, Bechtold WE, Ward JB, Wiencke JK: Susceptibility to Genetic Damage From Occupational Exposure to Butadiene. Proceedings of the International Symposium on Health Hazards of Butadiene and Styrene, 1993

Wiencke JK, Kelsey KT: Inter–Individual Sensitivity and Cytogenic Response to Diepoxybutane. Proceedings of the International Conference on the Health Hazards of Butadiene and Styrene, 1993

Bechtold WE, Kelsey KT, Ward JB: Measurement of 1,2–Dihydroxy–4–(N–Acetylcysteinyl–S)Butane In a Urine As a Biomarker of Exposure to 1,3–Butadiene. Proceedings of the International Conference on the Health Hazards of Butadiene and Styrene, 1993

Haefeli WE, Srivastava N, Kelsey KT, Wiencke JK, Hoffman BB, Blaschke TF: Glutathione S–transferase Polymorphism Does Not Modify Venodilatory Potency of Nitroglycerin in Human Veins. Clinical Science, in press, 1992

Cullen MR, Solomon L, Pace PE, Buckley P, Duffy T, McPhedran P, Kelsey KT, Redlich CA: Morphologic Biochemical and Cytogenetic Studies of Bone Marrow and Circulating Blood Cells in Painters Exposed to Ethylene Glycol Ethers. Environ Res, in press, 1992

Smith CM, Kelsey KT, Christiani DC: Risk Assessment and Occupational Health Overview and Recommendations. New Solutions, in press, 1992

Wiencke JK, Wara DW, Little JB, Kelsey KT: Heterogeneity in the Clastogenic Response to X-rays in Lymphocytes from Ataxia-Telangiectasia Heterozygotes and Controls. Cancer Causes and Control 3:237-245, 1992

Caggana M, Liber HL, Coleman MD, Mauch PM, Clark JR, Kelsey KT: A Prospective Study of *hprt* Mutant and Mutation Frequency in Treated Cancer Patients. Cancer Epidemiology, Biomarkers and Prevention 573-580, 1992

General Mortality & Cancer Incidence in Florida Pesticide Applicators

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Importance to Occupational Safety and Health

Pesticides are chemicals used since ancient times to destroy or control pests. Although the primary hazard to humans associated with pesticide exposure is acute poisoning, there has been considerable concern surrounding the possibility of pesticide carcinogenicity and other chronic health effects in humans. The pesticides which have generated the greatest concern for possible carcinogenicity include the herbicides (chlorophenoxy acids and chlorophenols), heavy metals (especially arsenicals), petroleum products (polyaromatic hydrocarbons), organochlorines, and fumigation agents (EDB, MethylBromide). This is important given the huge volume of pesticides now used throughout the world in agriculture, industry and in homes; in addition, there is concern with regards to the environmental and food residue contamination from pesticides which could lead to mass chronic low-level exposure.

Under EPA since 1970, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) has required that persons who buy or use restricted-use pesticides must be certified as competent pesticide applicators or must be directly supervised by a certified applicator. The State of Florida has computerized records of over 16,000 certified pest applicators for over 10 years and paper records for up to 25 years. In addition, as a highly agricultural and tropical state, Florida is a major pesticide user.

Objectives

The proposed study will be retrospective cohort analyses of the cancer incidence and general mortality, with a nested (synthetic) case control study of cancer incidence, among a cohort of the Florida certified pesticide applicators with occupational pesticide exposure in Florida for at least 20 years.

Because the greatest exposures to pesticides occur in the occupational setting, this study should add to the body of knowledge concerned with pesticides and their health effects in humans. Results from the study (i.e. specific cancer and other mortality rates, protective equipment use, and other risk factors) can be incorporated into existing mandatory educational programs of the Florida Department of Agriculture Bureau of Pesticides to prevent future illness in this and similar workforces.

Methodology

Cancer incidence since 1980 will be obtained by linking the data from the pest applicator licenses with the Florida Cancer Data System (FCDS). Mortality information will be obtained through the Florida Vital Statistics Death Linkage. In a nested (synthetic) case control study, exposure and relevant risk behavior data will be sought through the distribution of a questionnaire to selected cases of incident cases of cancer and a random sample of matched applicators as controls. Information concerning specific pesticide use, race/ethnic status, and possible confounding factors (such as tobacco use) will be obtained. Analyses will evaluate total cancer incidence and specific cancer incidences compared to age and sex adjusted state and national rates. In addition, risks for specific cancers associated with pesticide exposure will be evaluated, controlling for confounding variables such as tobacco use and using an internal cohort control group. Finally, cause specific mortality and cancer incidence experience of this cohort with national and internal comparisons will be evaluated.

Significant Findings

None to date.

Molecular Dosimetry for Carcinogens

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Importance to Occupational Safety and Health

Airborne levels of contaminants will not always predict dermal absorption, and in some occupations, dermal absorption may be the main route of exposure for many carcinogens in the workplace. Exposure to complex mixtures containing polycyclic aromatic hydrocarbons e.g., benzo(a)pyrene (BaP) and 7,12 dimethylbenzanthracene [DMBA]; N–heterocyclic aromatics e.g., 7H–dibenz[c,g]carbazole [DBC]; and aromatic amines e.g., 4–aminobiphenyl (4ABP), can cause tumors at the site for BaP, DBC and DMBA or at distant organs (as in the case of aromatic amine–caused bladder cancer or DBC induced liver cancer). Biomarkers sensitive to the effects of compounds absorbed dermally would increase our ability to predict significant exposure and early effect. The aims of our grant are to develop two such markers (DNA adducts and micronuclei (MN) frequencies) for proto–typical occupational carcinogens. This may help identify threshold levels of exposure for individual carcinogens that correspond to the limits of detection for combined adduct and MN measurements in the workplace.

Objectives

The kinetics of DNA adduct levels (^{32}P–postlabeling assay) and MN frequencies (cytochalasin–B blocking method) will be determined in mouse skin and liver for BaP, DBC & 4ABP respectively. Dose–response relationships will be established between carcinogen–DNA adducts and cytogenetic damage as measured by MN frequencies. Finally, the mechanisms of clastogenicity will be evaluated by using centromere–specific antibodies for MN formation in mouse skin and liver.

Methodology

The study has been divided into two main parts:

1. Kinetics Study – The kinetics study has been divided into two parts:
   (a) Dose response study (b) Time course study
   This study will allow for observation of repair and determine the times of maximum DNA binding and maximum MN expression.
2. Inhibitor study – An inhibitor of Cytochrome P–450 will be used to determine if MN formation could be inhibited. These experiments will enable us to understand the mechanism of MN formation.

Keratinocytes from treated and control animals will be isolated under sterile conditions. They will be resuspended in low calcium minimum essential medium and plated in collagen coated microscope slides at a cell density of 4 x 10^6 cells/slide. Once these conditions are established, similar studies will be carried out on hepatocytes. Hepatocytes from treated and control mice will be isolated in a dissociation medium containing collagenase in Hepes buffer, resuspended in Leibowitz (L15) or Williams WE medium and plated at appropriate densities in tissue culture plates. DNA from keratinocytes (scraped epidermal fragments from the dermis and stored at −80°C) and hepatocytes will be isolated using the phenol extraction procedure. DNA adduct levels will be determined by the ^{32}P–postlabeling assay. Approximately 10,000 micronuclei/dose will be scored in cytokinesis blocked keratinocytes and hepatocytes. Kinetochores of micronuclei will be stained with the primary and secondary antibodies in order to distinguish micronuclei formed as a result of aneuploidy as opposed to those formed as a result of clastogenicity.

Significant Findings

Conditions have been established for the isolation, growth and maintenance of keratinocytes in collagen coated microscope slides and petri dishes.

Methodology is currently being developed to isolate DNA and to improve its yield from epidermal fragments. Once the conditions are optimized, the DNA samples from treated and control animals will be used for ^{32}P–postlabeling. Preliminary experiments indicate that carcinogen–DNA adducts are present at the 50 μg/mouse dose.

Experiments were performed to optimize the conditions for obtaining maximal numbers of binucleate (BN) cells [MN are scored in 1000 cytokinesis–blocked binucleate cells]. It has been found that mouse keratinocytes have to be cultured, in the presence of cytochalasin–B, for

72 hours in order to obtain optimal numbers of binucleated cells.

Conditions have been optimized for performing the micronucleus assay. The BN fraction and the number of MN in acetone treated controls, *in vivo*, were 22 +/- 8.7 % and 12.5 +/- 6.7 respectively. *In vitro*, the BN fraction and the number of micronuclei in the controls were 22 +/- 6.3 % and 13.9 +/- 7.7 respectively. *In vitro*, the BN fraction and the number of micronuclei in the solvent (dimethyl sulfoxide) controls were 29.5 +/- 10.9 % and 10.5 +/- 2.4 respectively.

At the doses ranging between 4.5–50 μg/mouse, BaP does not produce a significant increase in MN over acetone treated controls [*in vivo*]. In addition, this compound does not produce a significant increase in MN *in vitro* [12μg – 120μg/ml of media]. However, adriamycin (*in vitro*) produces a very significant dose dependent increase in MN when compared to controls [25 ng/ml 99MN/1000 BN cells; 50 ng/ml 165 MN/1000 BN cells; 100 ng/ml 288 MN/1000 BN cells]. This indicates that mouse keratinocytes have the ability to express MN formation. This finding is further substantiated by the fact that DBC [*in vitro*], an equally significant environmental and occupational pollutant also induces a dose [0.01 – 2.5 μg/ml] dependent increase in MN [6.5–25.5 MN/1000 BN cells] over controls. Further experiments are underway to examine more closely the kinetics of MN formation by DBC and to determine if an association exists between adducts and MN for DBC as well as DMBA.

The lack of a response in mouse keratinocytes for BaP indicates that negative results in the skin MN assay should be interpreted with caution.

Cocarcinogenic Particulates in Coculture System

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Importance to Occupational Safety and Health

Pulmonary abnormalities are listed among the ten leading occupational diseases in the work place in the United States. Iron and aluminum compounds are widely encountered particles in the occupational settings. In addition to these particles, workers are frequently exposed to polycyclic aromatic hydrocarbons (PAH). Benzo(a)pyrene (BaP), a ubiquitous PAH has been well characterized over 70 years. The adverse effects of BaP are linked to its active metabolites rather than to BaP itself. It has been shown that iron oxide, but not aluminum oxide, can enhance lung tumor formation in combination with BaP. The purpose of this study is to explore the role of particles in the induction of pulmonary disorders, in particular, lung cancer. Male Syrian Golden hamsters (6–8 wks old) will be used in this study based upon: (1) low spontaneous lung cancer rate; (2) higher resistance to pulmonary infection and inflammation; (3) resemblance to humans in terms of histogenesis and pathogenesis. Primary alveolar macrophages (AM) and tracheal epithelial cells (a cell line provided by Dr. Mossmon from University of Vermont, Burlington, Vermont) will be cocultured. The reasons are that (1) biological responses to inhaled particles include their ingestion by AM and clearance from the lung; (2) both AM and tracheal epithelial cells have the capability to metabolize BaP; (3) the target tissue in terms of pulmonary carcinoma is associated with epithelial origins. The main focus of this project is to study the effect of particles upon the alteration of BaP metabolism and DNA binding. The profile of BaP metabolites, the amount and types of DNA–adduct formation may provide us with some insights upon the role of particles in the mechanism of cocarcinogenicity.

Objectives

The overall objective of this study is to investigate the role of particles in potentiating pulmonary tumorigenicity. The proposed hypothesis is that cocarcinogenicity of particles with BaP is due to the enhancement of BaP metabolism in AM and potentiation of the binding of BaP metabolites to the DNA of target epithelial cells. The specific aims are as follows: (1) to determine the alteration of basal metabolic activities of AM in response to BaP or BaP–coated particles (Fe_2O_3 and Al_2O_3); (2) to determine the pattern and amount of BaP metabolites, in particular, 7,8–diol–BaP, the precursor of the ultimate carcinogen, in response to radiolabeled BaP or BaP–coated particles in AM; (3) To determine the level of DNA–binding in epithelial cells which have been cocultured with AM in response to BaP or BaP–coated particles; and (4) to identify the profile of DNA adducts in epithelial cells in response to

cocultivation of AM which have been treated with BaP or BaP–coated particles.

Methodology

Cytochrome c reduction assay is used to measure the basal metabolic activity of AM. Ethyl acetate extraction and HPLC analysis are conducted to determine the pattern and amount of BaP metabolites in the cells. 32P–postlabelling is conducted to measure and identify DNA adducts in the cells.

Significant Findings

Viability (erythosin B dye exclusion) data suggest that up to BaP(5ug) coated 2.0mg Fe_2O_3 or Al_2O_3 particles /10^6 AM /plate revealed no signs of cytotoxicity. Within this dose range, metabolism studies were conducted with BaP(5ug) alone or BaP(5ug) coated particles (0.5,1.0,1.5 and 2.0mg). After 24 hr, metabolism data indicate that the release of dihydrodiols(9,10;4,5;7,8), phenols(9;3;7), quinones(4,5;3,6) and total BaP metabolites was significantly greater with Fe_2O_3 compared to Al_2O_3 or BaP alone. The formation of 7,8–dihyrodiol–BaP, the procarcinogen, was also consistent with the increase of Fe_2O_3 doses. Coadministration of 7,8–benzo(a)flavone (α–NF,5uM), an inhibitor of cytochrome P–450s, significantly reduced the BaP metabolism in BaP–coated Fe_2O_3 and Al_2O_3 treatments, 66% and 55%, respectively. These data suggest that particles enhance the metabolism of BaP in AM via the modulation of P–450s isozymes. Currently, cyclohexene oxide(CO), an inhibitor of epoxide hydrolase is also under investigation. The DNA from tracheal epithelial cells (HTE) which were coincubated with AM were isolated and quantitated. The treatments of these DNA samples include, BaP(5ug), BaP(5ug)–coated Fe_2O_3 (1.0mg)or Al_2O_3 (2.0mg), BaP(5ug)/α–NF(5uM), BaP(5ug)/CO(0.001M) and BaP(5ug)–coated Fe_2O_3 (1.0mg)or Al_2O_3 (2.0mg)with α–NF(5uM). ^{32}P–postlabeling assays are underway to identify the profiles of DNA adducts.

Explosion Hazards Related to Combustible Dusts

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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 1991, there were 16 dust explosions, 9 injuries, and 1 death. 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 FY 1981. Additionally, the number of injuries has declined steadily from a decade high of 59, also in FY 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.) This contrasts strongly with the traditional characterization of dust explosion hazards which employed "standard" testing apparatus in which well characterized dust was allowed to react under unknown and in some cases inappropriate conditions and where the results were characterized by parameters which may not be quantatively useful. Analytical efforts directed at the development of models which explain the observed phenomena have been productive.

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 thermodynamic 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 for cellosic particles, the volatile and char combustion rates have been established for both non and nearly spherical particles. Modification of the apparatus which allows multiple view imaging of the burning particle has been completed allowing the determination of a more accurate size shape history thus improving the burning rate data. The Premixed Turbulent Combustion Bomb has been modified to produce extremely high levels of nonsteady turbulence exhibiting some similarity to the more traditional dust explosion testing apparatus. The Laser Doppler Anemometer system has been adopted to acquire data under these transient conditions. The higher levels of turbulence have been verified as previously successful and strong ignition sources under these conditions do not lend to flame propagation. The layered dust experiments conducted in the Flame Acceleration Tube which was lengthened to seventy meters regularly produces deflagration to detonation transitions. The severity of the combustion process is indicated by overpressures varying from 30–60 atm, temperatures varying from 1600–1800 K, and velocities bracketed by 1120–1760 m/s. The exact results depend upon the dust layer pattern, moisture content, type, and intensity of the ignition source. The multiheaded structure of the detonation wave is currently being resolved. Finally, an instrument based upon forward and back scattered light has been developed which gives the rate of entrainment of the layered dust, which is presumably the rate limiting process. The analytical modelling of the accelerating flame supported by the layered dust has shown that such flames can generate higher overpressures than constant velocity flames. In the deflagration to detonation transition, the peak pressure occurs where the detonation originates, and after a short distance, a steady detonation is established. The direct initiation of a detonation fueled by layered dust by a strong ignition source has proved to be more elusive. However, with a strong initiating blast wave in a pure oxygen environment with a high layered dust concentration, an accelerating detonation wave could be generated behind the initiating blast wave. It is apparently difficult to rapidly suspend the layered dust in the small characteristic time available.

Publications

Austin PJ, Kauffman CW, Sichel M: Combustion of Single Non–Spherical Cellulosic Particles. Dynamics of Heterogeneous Combustion and Reacting Systems, Progress in Astronautics and Aeronautics AIAA, Vol 152, pp 136–154, 1993

Jarosinski J, Pu YK, Bulewicz EM, Kauffman CW, Johnson VG: Some Fundamental Characteristics of Cornstarch Dust Air Flames. Dynamics of Heterogeneous Combustion and Reacting Systems, Vol 152, Progress in Astronautics and Aeronautics, pp 119–135, AIAA, 1993

Sheng J, Tonello N, Kauffman CW, Sichel M, Wolanski P: Enhancement and Generation of Detonations Using Dust Layers. Dynamic Aspects of Explosion Phenomena, Vol 154 Progress in Astronautics and Aeronautics, AIAA pp 185–194, 1993

Kauffman CW, Sichel M, Wolanski P: Research on Dust Explosions at The University of Michigan. Powder Technology, pp 119–134, v 71, 1992

Sichel M, Kauffman CW: Dust Combustion. International Workshop on Heterogenous Combustion, Ministry of Science and Technology, The Dead Sea, Israel, January 6–10, 1992

Sichel M: Numerical Modelling of Heterogenous Detonations. Numerical Approaches to Combustion Modeling, (eds. ES Oran, JP Boris), Progress in Astronautics and Aeronautics, Vol 135 AIAA 1991

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

Case-Control Study of Sawmill Injuries in Maine

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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 work force. In 1987, the incidence of OSHA recordable injuries and illness 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, 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 is employed, in which cases are identified from employers' First Reports of Injury filed with the State Workers' Compensation Commission, collected for the U.S. Department of Labor Supplementary Data System. Controls are selected from employee lists provided by participating employers or from membership lists provided by participating union locals.

All subjects are interviewed to obtain information on demographics, anthropometry, work history and medical history. The interview also obtains information on production tasks, characteristics of the equipment, tools and product, and other features of the work environment. For cases, this information is obtained regarding the specific activities performed on a typical work day and at the time of the injury. Controls are 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 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 are also asked about the presence and activities of any workplace health and safety programs, such as worker training or labor–management committees.

Some supplementary exposure data is being sought, to attempt to validate the interview information. Where possible, the plant mechanics in participating mills are contacted after the interviews for additional specific information on equipment, tools and machinery. For a small number of workplaces, the investigators have visited 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 be 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

None to date.

Development of a Construction Injury Predictive Model

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Importance to Occupational Safety and Health

Analysis of previous injury data has been used to prevent injuries in other industries (such as manufacturing and transportation) in the past. As asserted by the National Safety Council (1982):

> Job safety analysis has proven time and again to be an accident and occupational illness prevention tool in many industries over the past years. (p. 2)

The ability to analyze accident data and predict the number of injuries that can be expected can make it possible for safety programs to be narrowly tailored to each specific construction project and contractor in order to make existing safety programs more effective in preventing injuries. Therefore the results of this study can greatly expand available knowledge about safety in the construction industry and lead to lower injury rates. Results of this research will be disseminated to the Occupational Safety and Health Administration (OSHA), the major construction contractor organizations (such as the Associated General Contractors, Associated Builders and Contractors, Mechanical Contractors Association and the National Electrical Contractors Association) for distribution to their membership, the Center for Excellence in Construction Safety, and the major insurance companies. The results of this study will be published in the relevant journals. (such as the "Constructor" and "Builder & Contractor").

The results of this research will provide the construction safety research community, contractors, insurance companies, risk managers, and OSHA a tool that can help measure the effectiveness of safety programs. Specifically, it will also enable OSHA to target projects with high risk factors for inspection and more aggressive prevention programs. Finally, the results will also serve as the basis for future research on developing injury predictive models for other categories of construction (residential, industrial, heavy and highway).

Objectives

The purpose of this research is to develop knowledge that can be used in preventing traumatic injuries at commercial construction sites. The main objective of this study is to develop a parsimonious empirical model that will have good capabilities of predicting the incidence of traumatic injuries requiring medical care among construction workers employed by commercial construction contractors. The first aim is to investigate and identify the most significant risk factors that can influence the occurrence of injuries at commercial construction sites. The general categories of risk factors to be addressed are characteristics of commercial construction contractors, projects and workers. The second aim is to analyze these categories of risk factors and understand the relationship between them and the number of traumatic injuries at commercial construction sites requiring medical treatment by a licensed caregiver. The third aim is to utilize these factors and their functions in a model that will have good capabilities of predicting the incidence of injuries at given construction sites before the commencement of that project.

Methodology

The main outcome of interest will be the rate of traumatic injuries occurring at commercial construction sites that require medical treatment by a licensed caregiver. The injuries studied will be the same as those that are required to be reported by OSHA. Data will be collected for a minimum of 100 commercial construction contractors and 400 projects from commercial construction contractors and the State of Washington Department of Labor and Industries, and a data base created. Risk factors focussing on specific characteristics of construction contractors, projects and workers will be analyzed.

Analysis will involve fitting Poisson regression models, with adjustment for overdispersion, and for shared contractor and project effects. Model fitting will be accomplished using the GLIM Computer Software, developed by the Royal Statistical Society. The characteristics of commercial construction contractors, projects, and workers will be investigated as explanatory variables in order to determine their significance in predicting injuries. Rates of injuries will be calculated as injuries/FTE. Relative risks and corresponding confidence intervals will be estimated for combined injuries, and for individual types of injury. Standard likelihood methods of generalized linear models will be used for testing the effect of each explanatory variable on the injury rate, both alone, and adjusted for the confounding effects of other explanatory variables.

Significant Findings

None to date.

Role of Postural Stability in Industrial Falls

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Importance to Occupational Safety and Health

Falls have been found to be a significant contributor in causing lumbar spine injury, fracture of bones, and disability. A review of occupational injury data in U.S. industries and those in other countries indicates that the construction industry has the highest incidence rates of accidents, including fatalities, among major industries. As per literature review, various field studies have identified several risk factors as contributing to falls at the workplace. These are: Environmental (surface contamination and friction, standing surface firmness and lighting); Job–Task (blocking of peripheral vision due to poor work layout and workload); and Personal (age, sex, and physical fitness level) factors.

This ongoing study will help identify and quantify the influence of individual and combination effects of Environmental, Job–Task and Personal risk factors on fall potential. The results from the proposed study will help develop a statistical model showing relationship between fall potential and the independent variables characterizing the Environmental, Job–Task and Personal risk factors. In future field studies, use of the statistical model to help evaluate the fall potential can be accomplished by measuring, in a walk–through evaluation, existing risk factors at the work site. The model can then be used to determine which of the risk factors need to be corrected to reduce the fall potential. Availability of such models will have significant impact in identifying risk factors and their reduction will help prevent fall–related injuries, disabilities, lost work days, and higher medical costs as well as increasing national productivity.

Objectives

1. To measure the upright postural balance (stability or sway) under different standing surface contamination conditions (dry/clean and oily), standing surface firmness (firm and compliant), environmental lighting (good and poor), and peripheral vision conditions (blocked and unblocked) after being exposed to different workloads (40 watts and 100 watts) in workers in the age range of 21 to 55 years.
2. To investigate the age–associated differences in the maintenance of upright postural balance under above mentioned risk factors.
3. To investigate the age–associated differences in postural corrective responses to: (a) sudden perturbation in the body segment movement; (b) forward reach and lifting; and (c) sudden external loading under all combinations of risk factors.
4. To investigate the age–associated differences in the relationship between an objective measure of

postural instability and the subjective perception of postural instability, under all combinations of risk factors.

Methodology

In this study, postural instability and fall potential of risk factors are being evaluated for industrial workers' performance (21 to 55 years of age) on 32 test conditions which represent combinations of these risk factors. These tests simulate conditions which occur in industrial/occupational environments. The current pool of industrial subjects represent a wide range of occupations. Subjects are tested immediately after exposure to light and moderate–to–heavy workloads (bicycle ergometer) to quantitate their postural stability. Before and immediately after completion of a workload, the subject is tested for upright postural sway and postural corrective responses to simulated tasks which might occur in an industrial environment. Also, their subjective perception of postural balance is assessed immediately after each test using a subjective Scale of Rating of Perceived Sense of Fall. The postural stability is measured with a six–component force platform located inside our Fall/Stability Assessment Facility. Each subject's "Functional Stability Boundary" is also determined. This information is used for the calculation of the Index of Proximity to Stability Boundary (IPSB). The value of IPSB obtained during the postural stability tests is used to determine which of the test conditions pushed the body's center of pressure (CP) to or beyond its stability boundary and, therefore, had the potential to create an accident due to a fall or near fall.

Significant Findings

The data are still being collected from the subjects therefore the findings presented are preliminary in nature. A quantitative method of characterizing fall potential has been developed and is being used to determine the effectiveness of this technique with the data from this ongoing study. A preliminary analysis of the data collected from the 38 subjects (complete data set from 46 subjects have been collected but all of them have not been analyzed yet) who have completed the testing protocol (providing data from 8,492 postural tests) has been performed. Despite the small sample, all conditions (workload,surface firmness, surface slipperiness, lighting and peripheral vision) already show a significantly ($p<0.05$) detrimental effect on postural balance as measured by the sway length parameter in a repeated measure analysis of variance. Each of these significant effects are consistent with our proposed hypotheses. Certain interactions among the experimental conditions or between age or gender and the within–subject conditions are also significant. For example, a significant lighting/surface firmness interaction indicated that subjects had even more difficulty while standing on a compliant surface in dim lighting than would be expected from either of these factors alone.

Workplace Assault-Related Injuries: Incidence and Risk

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Importance to Occupational Safety and Health

The Occupational Safety and Homicide Act was created in order to "assure as far as possible every working man and woman....safe and healthful working conditions and to preserve our human resources." Though occupational injury has changed significantly since the enactment of the OSHA Act by Congress, no specific portions of the act deal directly with intentional injury in the workplace. The potential for workplace violence, an increasing public health issue, threatens many employers and employees.

Occupational homicides account for 7,000 to 13,000 deaths per year, based on estimates from various data sources. In a recent NIOSH update, it was noted that occupational injuries affected minority groups in high–risk occupations disproportionately (19% black and 6% other races). Differences between men and women at work were also highlighted: while homicide at work accounted for 10% of deaths among men, it was the leading cause of death for women at work (41%).

Employees of high–risk industries previously Identified (convenience food stores, discount retail stores, gasoline service stations, eating and drinking establishments, and taxicab companies) continue to bear the brunt of assault–related injuries and fatalities. Most of the research in this area has focused on workplace homicides, yet the magnitude of non–fatal assault–related injuries has not been

assessed. Thus far, no specific risk factors or standards on preventive strategies for these industries have been developed.

Objectives

The overall objective of the proposed research is to understand the magnitude and identify the determinants of workplace assault–related injuries. To accomplish this objective, two specific aims are being undertaken: (1) to estimate the average incidence rates of fatal and nonfatal work–related assault injuries in seven California counties between January 1993 and June 1994; and (2) to identify individual occupational and environmental predictors of fatal and non–fatal assault–related injuries in selected high–risk occupations in the same seven California counties.

Methodology

The study design consists of two components:

1. Incidence determination and rate estimation based on a number of sociodemographic, occupational, environmental and industrial group parameters; and
2. A case–control study to identify risk factors for fatal and non–fatal assaultive injury.

We have expanded the study to encompass most of the conurban areas within the counties of Sacramento, Alameda, Santa Clara, Los Angeles, Riverside, San Bernardino and San Diego, California. The scope of our collaborative network now includes police, sheriff and coroner's departments, Cal–OSHA, and State Compensation Insurance Fund. This network of data sources serves an important role in linking health information to allow more precise estimates of work–related assaults and homicides.

We successfully piloted a detailed survey instrument for assessing factors surrounding assault–related violent incidents resulting in mild to severe injuries or fatalities. The survey is currently being implemented in all seven counties by field researchers, each of whom has received extensive training in survey administration and case– and control–finding protocols. Our field research staff has been equipped with a portfolio that contains letters of support from various members of the state legislature and from Cal–OSHA.

Case ascertainment procedures have evolved with recognition of the budgetary crisis affecting state and federal agencies. Additionally, some unforeseen delays in case surveys have surfaced: irreparable damage to business establishments following some violent incidents, permanent closure of small businesses where the victim was the owner, language barriers, and refusals to participate. For control finding, we are utilizing a database of business names, addresses, phone numbers, and contact persons across an identical spectrum of industries.

Significant Findings

None to date.

Vibration Oculomanual Coordination and Traumatic Injuries

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Importance to Occupational Safety and Health

The focus on manual control perturbation resulting from vibration exposure as a potential risk factor is of particular importance. Indeed, performance of visually guided motor activities is an important factor of accidents involving falls, dropping objects and improper use of controls. Furthermore, an estimated 1.45 million workers use vibrating tools and disabling injuries numbered 570,000 for mining, construction and manufacturing industries where vibrational hand–tools and vibrating machines are intensively used. Although one cannot blame vibration as a common denominator to those injuries, a significant number is likely to be related to manual control impairment resulting from vibration exposure.

The aim of this project is to contribute to the reduction of risk of acute occupational traumatic injuries associated with vibration–induced alterations of oculo–manual coordination. The proposed work will model eye–hand performance and the withdrawal reflex responses as a function of vibration frequency, displacement amplitude and exposure time of vibration applied to the hand.

The expected results will be used to estimate a vibration limit relevant to manual performance effects. Further disclosure of the importance of visual control of the limbs should lead to the

formulation of safety and design recommendations concerning the placement of controls and handles.

Objectives

The overall objective is to emphasize the often ignored or neglected role of movement errors in accidents occurring in vibratory environments. The general hypothesis is that vibration–induced modification of sensory messages, used by the central nervous system to control and regulate sensorimotor activities, contribute to the alteration of both movement accuracy and oculo–manual coordination. The following hypotheses are tested:

1. Involuntary motor activities, such as reflexes, are significantly affected during vibration,
2. Sensory perception is significantly affected by vibration,
3. Oculo–manual coordination is significantly affected during vibration,
4. Vibration–induced alterations persist after exposure and vary with intensity,
5. Permanent visual control of the upper limbs should compensate to some extent vibration–induced affection of other sensory modalities and contribute to performance improvement,
6. Vibration displacement amplitude should exhibit a high correlation with performance decrement over the 80–200 Hz frequency range,
7. Sensorimotor performance should be less affected by high frequency vibration (> 200 Hz)

Methodology

Withdrawal reflex

This protective muscular response, elicited in the forearm flexor muscles by electrical stimulation of the radial nerve at the wrist is studied during low level grip exertion (at rest or 10% MVC). Electrical activity of the fingers and wrist flexor and extensor muscles are monitored using pairs of small cupular electrodes. Hand vibration (90, 150, 200 Hz, 0.2 mm) is applied perpendicularly to a vertical handle held by the subject. Changes in the amplitude of both components of the reflex responses are quantified as a function of vibration parameters.

Manual dexterity

Manual movement precision and performance time are evaluated through a visuo–manual tracking task performed before and after long term hand vibration exposure (90, 150, 300 Hz, 0.2 mm and 0.3 mm, 10 min. duration). The alterations of tracking errors and tracking time are analyzed as a function of the vibration parameters.

Oculo–manual coordination

A pointing task consisting in aiming simultaneously with the hand and the eye at visual targets is performed before, during short term hand vibration exposure (200 sec) and after long term hand vibration exposure (10 min.). The vibration frequencies are 90, 150, 300 Hz, the amplitude is 0.2 mm. Eye and hand position are measured to quantify ocular and manual performance. Eye movement pattern is analyzed to evaluate oculo–manual coordination. The influence of vibration parameters is analyzed.

Significant Findings

Withdrawal reflex

Motor effects – Both components of the reflex response are facilitated by hand vibration and this facilitation increases with initial muscle contraction; however, each component is affected differentially by vibration frequency. For the early component, the facilitation is significantly less pronounced for a 200 Hz vibration, while for the late component vibration frequency had no significant effect.

Effects on perception – When the muscles were initially at rest, a decrease in perceived discomfort elicited by the electrical stimulus was indicated by 7/10 subjects during vibration exposure. When a moderate level of voluntary contraction was exerted the differentiation between pre and per–vibration sensation evoked by the electrical stimulus was not statistically significant.

Manual dexterity

Vibration induced a significant increase in errors and a significant decrease in tracking time. These impairments decay with time after vibration exposure. The recovery period is greater than 5 min. but less than 10 min. The subjective rating of the performance indicates that the subjects tend to perceive the task as being easier after vibration exposure. Thus, the results show that vibration affects precision and velocity control of visually guided hand movements and that performance decrements are not perceived. Vibration frequency and amplitude do not seem to have a strong influence.

Both studies indicate that vibration–induced alterations of involuntary or voluntary motor activities are not consciously perceived.

Ergonomics of Task Performance On Slippery Surfaces

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Importance to Occupational Safety and Health

Previous studies have shown that the event which immediately led to injury was slip in about 50% of the cases. This type of underfoot "first event" has been the main contributor to falls. The proposed study provides an experimental design which has the potential for investigating the interaction between age, sex and other fall risk factors such as psychophysical aspects of slipperiness evaluation, objective measure of surface slipperiness, shoe wear/tear, and lighting, while performing simulated industrial tasks. The proposed study will provide dynamic coefficient of friction (DCOF) and the rate of change in DCOF as criteria for slip prevention for (1) dynamic task performance while standing on a slippery surface and (2) walking with and without a turning motion with a weight in hand. Additional information will be provided regarding the change in the above criteria when wearing a used shoe with a worn–out sole surface in a young and an older age groups of workers. The gait pattern characteristics can significantly influence the required DCOF demand which provides the necessary slip protection. This type of information will have significant impact on the development of better portable slip–testing devices which can be used in a more realistic manner at the worksite (such as, the use of worker shoes which were involved in a slip–related accident) and can measure appropriate variables which better predict slips at the workplace. The evaluation of any slip–testing device as described above is dependent on the assumption that human performance on slippery surfaces is influenced by only limited biomechanical factors without regard to environmental, psychophysical and personal risk factors.

While slip potential is predicted by DCOF and rate of DCOF the fall potential is influenced by additional factors such as Job, Environmental and Personal factors. For example, Personal factors of age, postural muscle strength, reaction time, subjective ability to correctly assess slipperiness of surface (psychophysical aspect) and gait patterns can significantly dictate whether task performance on a slippery surface will produce a fall or not.

Objectives

1. To determine the relationship between subjective assessment of slipperiness and the objective measure of coefficient of friction under optimal environmental lighting, job–task, and shoe sole wear/tear conditions. Also, determine the age–associated influence on the above relationship.
2. To determine the effect of nonoptimal conditions of environmental lighting, job–task, shoe sole wear/tear and the subject's age on her/his ability to correctly assess the slipperiness of a surface.
3. To determine the effect of environmental lighting, job–task, shoe sole wear/tear conditions, and age on the subject's ability to perform tasks (of daily living and occupational nature) requiring demands on her/his static (upright balance) and dynamic (gait) postural balance while her/his shoe sole surfaces are in contact with a slippery surface. To determine the age–associated differences in postural balance and gait characteristics associated with task performance on a slippery surface.
4. To identify and quantitate postural balance (for both static and dynamic tasks) variables relevant for assessing the fall potential associated with task (of daily living and occupational nature) performance on slippery surfaces under various combinations of environmental lighting, job–task, and shoe sole wear/tear conditions.
5. To determine the characteristics of the required coefficient of friction values and body segment movement dynamics for performing tasks without slipping under various combinations of environmental lighting, job–task, and shoe sole wear/tear conditions.

Methodology

In the proposed study, gait and postural instability and fall potential of all risk factors will be evaluated for industrial workers' (21 to 59 years of age) task performance on a slippery surface. These tasks simulate conditions which occur in nonoccupational and occupational environments while standing or walking on a slippery surface. The upright postural sway test (stability) and tests of postural corrective responses to the testing of upright postural balance, rapid movement of body segment, and

forward/upward reach during lifting will be administered under all combinations of the following test conditions. After the postural stability test, the subjects will undergo gait evaluation tests with and without a five pound weight in hand under all combinations of the following three test conditions. Condition 1: Three levels of randomized slippery surface (low, medium and highly slippery). Subjects will know that the surface is slippery but will be without the knowledge of its degree of slipperiness. Condition 2: Under acceptable (good) or unacceptable (poor) environmental lighting as per American Illuminating Engineering Society guidelines for rough to moderately precise work. Condition 3: Shoe conditions will be not worn–out sole (new) and worn–out sole. The order of administration of postural stability and gait tests will be randomized. An initial baseline measure (standing on a dry, nonslippery surface) will be performed before the twelve randomized combinations of these conditions. All subjects will undergo the test of Estimated Maximum Displacement of Center of Pressure (EMAX) before initiating the series of Postural Balance Tests and Gait Tests. The results of the EMAX test will provide an estimate of each subject's stability boundary in the anterior direction and the "Functional Stability Boundary" will be quantified. After the EMAX tests, each subject will return to the laboratory for additional visits to perform postural stability and gait tests. Before initiating the postural balance and gait tests each subject will undergo subjective assessment of slipperiness test. During subjective slipperiness assessment test, postural stability test and gait test each subject's insole pressure distribution will be also measured. The postural balance will be quantitated with a six component strain gauge force platform and the three dimensional gait characteristics will be measured with a video–based motion analysis system.

Significant Findings

None to date.

Safety First: Fault Tree Expert System For Construction

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Importance to Occupational Safety and Health

The project develops a system to improve construction safety by emphasizing the engineering aspects, and further incorporates other aspects pertinent to the engineering control system (e.g., procedural, behavioral, social, and economic aspects) The importance of the work is as follows:

1. The knowledge gained could have a great impact on the way occupational safety and health institutions perform an analysis of a construction accident. These institutions are constantly involved in promoting safety in construction and in performing investigations in the event of construction accidents. The product of our research can be used as an engineering control system and would be of an invaluable aid to these institutions in reaching their objectives.
2. We expect that research results will affect existing procedures and will automate the processing of construction accident information When completed, our project produces a run–time version of a software for use in micro computers. The system can be stationed centrally or distributed to any construction site. The service life of the system is essentially unlimited.

Objectives

Our objective is to develop SAFETY FIRST, a fault tree expert system for investigating and avoiding construction accidents in the area of construction falls. It is expected that the system could be used to minimize construction accidents and improve construction safety. SAFETY FIRST will provide a heuristic yet systematic approach for investigating the causes of construction accidents and for reducing and

avoiding them, thereby increasing labor safety. The research is intended to accomplish the following:

1. To provide the user a tool with which to investigate a construction accident that has already occurred. The fault tree models will establish all possible causes contributing to the accident (and any combination of these causes), and will rank them in order of importance. Based on evidence gathered from the accident site, the expert system will trace a particular cause and will explain to the user how and why the accident has occurred. The expert system will also recommend ways to avoid this accident in the future.
2. To provide the user with consulting tool that will explain the contributing causes of potential construction accidents. The fault tree models will show graphically the relationships among these causes and will determine the potential "weak links" that could result in a construction accident. Simulation study by the user using the expert system models will establish which causes are potentially hazardous to the workers. Hence, the system will serve as a tool to warn the user of potential accidents and to suggest applicable precautions.

Methodology

In order to achieve the objectives of our proposed project, we will use and combine two innovative research methods: the fault tree system and the expert system. Fault tree models are employed to represent the knowledge obtained from experts and literature concerning the causal relationships among events/causes that contribute to a construction accident. In simulating the way experts determine the cause of the accident, the expert system accommodates the knowledge for use by safety investigators. The research encompasses the following four major tasks: (1) Knowledge acquisition, (2) Fault tree development, (3) Expert system development, and (4) Validation.

During the knowledge acquisition process, we function as the knowledge engineer who communicate with the experts, gather information from literature, and build the knowledge base. We perform three phases of knowledge acquisition: preliminary discussion, detailed discussion, and organization. Expert knowledge are represented by fault tree models, which show the paths of knowledge an expert takes in reaching a conclusion. Development of fault tree models include fault tree logic evaluation, fault tree modeling, and analyses. The development of the expert system includes knowledge base development and system validation. The knowledge acquired from experts and literature is organized in each path. A piece of knowledge can be rewritten in IF–THEN statements, which represent the way an expert assesses the cause(s) of an accident—i.e., heuristically. These assessments are often based on an expert's rules–of–thumb, educated guesses, and assumptions based on the expert's experience in construction safety. Knowledge from research literature on safety, including codes, regulations, and construction safety practices, can also be represented by IF–THEN statements much the same way as that from experts. These statements will be compiled and translated into IF–THEN production rules using the production rule language The production rules will be accommodated in a knowledge base, an essential part of am expert system. Evidence or information furnished by a user will be matched with a rule to produce the basic causes of a fall. The knowledge base of SAFETY FIRST will be validated by the knowledge engineer, participating expert(s), and non–participating experts.

Significant Findings

To date, we have completed the knowledge acquisition and representation of SAFETY FIRST. The knowledge acquisition includes researching literature and selecting and meeting with experts Most articles we encountered during our study are brief reports or news releases of construction worker's accidents, statistics of such accidents, and regulations and codes to avoid these accidents. Although injuries, illnesses, and deaths during construction occur at a rate that is 54% higher than the rate for all industries, our literature study reveals that causes of construction worker's accidents, and in particular, construction falls are seldom discussed in detail.

The knowledge acquisition also includes obtaining information about construction falls from experts, who because of their experience, are knowledgeable in this domain. Experts elaborated on specific causes and their experience in solving past fall cases. Our findings reveal that experts' knowledge provides a wealth of information concerning construction falls that is often unavailable in literature.

We classified construction falls as falls from higher elevation, falls from same elevation, and slips (not fall). The platforms where falls could occur were categorized into floor openings, floor edges, wall openings, roofs, steel beams, top of walls, ladders, and scaffoldings. We analyzed all possible events that may cause the fall and represent them using fault trees. The results of our study confirm our earlier prognosis of using fault tree diagrams to best represent the structure of experts' knowledge.

Analysis of Construction Tasks For Overexertion Injuries

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Importance to Occupational Safety and Health

Overexertion injuries are the single largest classification of injury in construction, accounting for about 24% of all injuries. The Bureau of Labor Statistics and OSHA define overexertion injuries as "nonimpact cases in which the injury resulted from excessive physical effort, as in lifting, pulling, pushing wielding, or throwing the source of injury. Includes conditions resulting from repetitive motion in the use of hand tools".

Overexertion injuries generally occur as a result of performing a given task as planned. While overexertion injuries are not intentional, the underlying causes of the injuries are built into the prescribed tools and work methods. If the causes can be identified, it should be possible to engineer them out of the work. Once afflicted with an overexertion injury, many construction craft workers can be excessively challenged by the physical demands of their jobs. If the worker has the requisite skills and if alternative less–demanding employment is available, the worker can seek a different job where demands are better matched to physical capacity and ability. If alternative work cannot be found, the injured worker faces the dilemma of continuing at a job that causes excess fatigue or discomfort, or perhaps dropping out of the workforce.

Construction injuries have been categorized in many ways, including by trade (e.g. carpenters, electricians, laborers, etc.) but no attempt has been made to identify a causal relationship between specific tasks within a trade and the associated overexertion injuries. For example, carpenters account for 17% of all injuries and illnesses, but carpenters perform many fundamentally different tasks such as erecting concrete formwork, installing suspended ceilings, hanging drywall, etc. Carpenters who install formwork for concrete experience high rates of tendinitis in their elbows from banging the forms and connectors with hammers, carpenters who install suspended ceiling systems experience neck and shoulder problems from constantly looking and reaching up, and carpenters who hang drywall often suffer nerve damage in their hands from the vibration of the screwguns used to fasten the drywall to the framing system. All of these injuries fall into the general classification of overexertion injuries to carpenters, but the underlying causes are quite different and they call for fundamentally different types of workplace intervention.

The goal of this project is to identify specific construction tasks which place craft workers at high risk for overexertion injuries and disorders. High risk tasks can then be identified so that ergonomic and administrative principles can be applied to modify the task or work environment to accommodate human capabilities and limitations.

Objectives

The objective of this project is to analyze construction tasks for the presence of seven generic risk factors for overexertion injuries and to identify high risk tasks for possible ergonomic or administrative intervention. The hypotheses to be tested are that it is possible to identify the underlying risk factors for overexertion injuries for many specific construction tasks and that it is technically and economically feasible on many construction tasks to reduce the level of physical demands placed on craft workers.

Methodology

Overexertion injury data are currently reported by construction trade. No attempt has been made to determine which specific tasks within each trade place workers at high risk. This study will analyze each specific construction task for the presence of seven generic risk factors for overexertion injuries: repetitive exertions, static exertions, forceful exertions, localized mechanical stresses, posture stresses, low temperature, and vibration. Ratings for each risk factor will be made on a three point scale: Insignificant – The job is free of potentially harmful ergonomic stresses in the risk factor of interest. No corrective actions are necessary; Moderate – The job has stresses in the risk factor of interest that could be problematic (i.e. cause fatigue and/or injury) for some workers. Additional analyses using more precise methods should be used to determine the necessity for intervention; and High – The job has significant stresses in the risk factor of interest that are likely to cause fatigue and/or injury in some workers. Additional analyses and interventions should be taken

at a high priority. This study will identify particularly high risk tasks for ergonomic or administrative intervention. The ratings will be shared with the participants to help establish priorities for intervention or more detailed analysis.

Significant Findings

None to date.

Development of a Work Safety Scale

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Importance to Occupational Safety and Health

The National Safety Council (NSC) estimated that the total cost of industrial accidents in 1990, including insurance administration costs, wage losses, and medical costs, was 63.8 billion dollars (NSC, 1991). Millions of dollars annually could be saved if the number of accidents was decreased.

Fewer work related accidents have been linked to employees who perceive their jobs as relatively safe. These same employees report experiencing less anxiety, stress, and exposure to environmental hazards, all of which have been linked to accident rates. Therefore, the perceptions of the work environment and safety are correlated. By assessing the perceptions of employees, companies can alter the workplace and decrease the likelihood of accidents.

There are four existing measures of workplace safety perceptions: The Occupational Hazards Survey (Guastello & Guastello, 1988); Safety Climate Scale (Zohar, 1980); Physical Demands and Dangers scale, a sub–scale of the Job Stress Index (Sandman, 1992); and the Perceptions of Workplace Hazards Scale (Smith et al., 1992), though they are not comprehensive nor psychometrically sound. The reliability and validity of each instrument is not well established, and no measure adequately taps the domain of workplace safety. Thus, there is a need for a comprehensive and psychometrically sound instrument to assess issues of workplace safety.

Objectives

The aim of the present research is to complete Phase I of the development of a questionnaire assessing employees' attitudes toward workplace safety. The proposed instrument will: (a) possess adequate psychometric integrity – reliability and validity information; (b) comprehensively assess important dimensions of perceptions of workplace safety; and (c) be easy to complete. Scores on this measure will assist decision–makers in industrial settings to: (1) predict the extent of accidents; (2) determine the need for workplace safety programs; (3) help organizational officers design specific workplace safety programs to address specific employee concerns; and (4) determine the effect of such safety programs.

The series of proposed studies is designed to develop and validate a measure of workplace safety, the Work Safety Scale (WSS). The WSS will be designed to assess five dimensions of work–related safety: perceptions of job safety; coworker safety; supervisor safety; management safety; and satisfaction with the safety program. This multidimensional approach to safety assessment is necessary because ample evidence exists that work safety is not a unidimensional construct.

Methodology

For each of the five scales of the WSS, descriptive adjectives or phrases will be written to tap into relevant content domains. For each item, respondents indicate the extent to which they agree that the item describes their job situation using a five–point Likert scale 1 – Strongly Disagree to 5 – Strongly Agree). An attempt will be made to counterbalance the number of positively phrased items with negatively phrased items. Twenty–two to 29 items have been written for each of the sub–scales being developed, with the expectation that, after item analysis, at least half of the items will be retained for the final form of the instrument.

Two studies will be conducted. The first will assess the distribution of scores for each scale item, the factor structure of the items, item statistics (means, corrected item–total correlations) and the internal consistency of the subscales. This study will be used to retain items that possess good psychometric characteristics. The second study will be conducted to provide a cross–validation of the findings of the first study. Specifically, for the second study, retained scale items will be administered to an independent sample of subjects, and item statistics (item means and corrected item–total correlations) will be calculated. Additionally, a factor analysis will be conducted on

all items in Study II and internal consistency estimates will be calculated for each subscale.

The WSS will consist of 124 items, reflecting the five content areas described above. The respondents are to indicate, for each item, how strongly they agree that the word or phrase describes their job (1 – Strongly Disagree to 5 – Strongly Agree).

Approximately 700 patients seen at Medical Consultants Northwest, Inc. (MCN) will serve as subjects in the first sample. These patients will be seen at MCN for independent medical evaluations. In addition to the paperwork they normally complete, patients will also be given the WSS. Their responses on the WSS will remain anonymous.

An independent sample of respondents will be used in Study II. The approach to obtaining subjects used in Study I will be used in Study II. The approximately 700 respondents will be asked to complete the initial items of the WSS, along with other information, including occupational title, educational status attained, shift work status, sleep complaints, physical complaints, and psychological complaints. The additional information will be used to provide evidence of the validity of the WSS.

Significant Findings

None to date.

Vascular Effects of Chelation In Lead Exposed Workers

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Importance to Occupational Safety and Health

There is growing evidence from epidemiological and animal studies that low-level exposure to lead may result in increased blood pressure, a major risk factor in the development of cardiovascular, cerebrovascular, and renovascular disease. From both a physiologic and public health standpoint, black adults appear particularly susceptible to the hypertensive effects of lead, and constitute a key target group for initial clinical investigation. In our group's recent cross-sectional study of San Francisco busdrivers, a strong relationship between lead and blood pressure was found exclusively in black subjects. Other studies have found black hypertensives to have an elevated pressor response to infused catecholamines, and to have higher intracellular stores of calcium, the same mechanisms experimentally implicated in lead's blood pressure effects. Although black adults constitute a key susceptible group, large epidemiological evaluations, such as NHANES II, have found a positive association between lead and blood pressure in non-black subjects as well.

Most investigations of the effect of lead on blood pressure and other health outcomes have relied on blood lead as a biomarker of exposure. However cumulative lead exposure may be better assessed by measurement of lead in bone, where greater than 95% of the adult body lead burden occurs with a half-life of several years. The availability of K x-ray fluorescence as a noninvasive quantitative measurement of the lead concentration of cortical and trabecular bone may enhance the investigation of dose-response relationships in lead-associated disorders. In addition, the recent availability of the oral chelating agent 2,3 dimercaptosuccinic acid (DMSA) permits implementation of an outpatient chelation challenge test to investigate the relationship between bone lead stores and the"mobilizable" pool of lead that may be most closely associated with toxic effects on target tissues.

Objectives

The research objectives are to assess cumulative lead exposure by K x-ray fluorescence, and to elucidate the mechanism of lead's vascular effects in a subset of lead exposed subjects with borderline to moderate hypertension. The latter aim will be approached by determining whether a reduction in soft tissue lead burden by EDTA chelation will reduce the pressor response to infused norepinephrine. The relationship between chelatable lead and bone lead burden will be explored using an outpatient chelation challenge test.

Methodology

K x-ray fluorescence measurement of lead in bone is determined noninvasively with an Abiomed Body Lead Analyzer. In this technique, the tibia (representative of cortical bone) and the patella (representative of trabecular bone) are sequentially irradiated with low energy photons from a ^{109}Cd source, and a germanium detector quantifies fluorescent x-rays with energy characteristic of lead K-shell electron transitions. The lead fluorescence signal is normalized to the elastic, or coherently scattered x-ray signal, yielding a measurement of bone lead concentration expressed as micrograms of lead per gram of bone mineral (ppm).

To investigate the effect of lead chelation on vascular responsiveness, asymptomatic subjects with blood lead concentrations between 15 and 80 μg/dl, are recruited as subjects from industries, unions, and occupational and environmental health clinics. Black adult men are specifically targeted for recruitment. Subjects with diastolic blood pressure between 85 and 105 mmHg on two consecutive screenings, indicative of borderline to moderate hypertension, are admitted to the UCSF General Clinical Research Center, concurrent with outpatient and inpatient stabilization of dietary sodium. In each of 2 intervention cycles, subjects receive a stepped-dose infusion of norepinephrine (NE), immediately before and after an experimental intervention, and the slope of the dose-response lines is assessed. In one cycle, the intervention consists of a 48-hour lead chelation with i.v. EDTA, in the other matched i.v. placebo. The order of the two cycles is assigned in a double blinded, balanced manner. For each subject, the change in slope between the pre- and post-intervention NE infusion, a measure of the change in pressor sensitivity, is compared between the chelation and placebo cycles.

To assess the relationship between "chelatable" lead and bone lead, selected subjects with

occupational lead exposure will collect urine specimens before and after an out–patient challenge dose of the new oral chelating agent, dimercaptosuccinic acid, (DMSA, succimer). The relationship of urinary lead to bone lead concentration measured by K x–ray fluorescence will be investigated using regression models.

Significant Findings

Normative data on K x–ray fluorescence measurement of bone lead concentration has been collected on 100 subjects, age 11 to 78, with limited occupational lead exposure. Results revealed that log transformed tibia (cortical bone) and patella (trabecular bone) lead concentration were highly correlated with age ($r = .71$, $p < 0.0001$; $r = .65$, $p < 0.0001$). An age–sex interaction existed, resulting in higher bone lead concentrations in older males. Blood lead concentration (mean 5.72 ± 3.98 μg/dl), was not correlated with age. Log blood lead was weakly correlated with log of tibial lead ($r = .23$, $p = .02$) and patella lead ($r = .33$, $p = 0.001$). A piece–wise linear regression model in age and sex yielded $R^2 = .60$ for tibia lead, and $R^2 = .55$ for patella lead. An expanded model for tibia lead ($R^2 = .66$) revealed that smoking history was significantly associated with an increased bone lead concentration, and among females, a history of ever having nursed an infant was associated with lower bone lead. These models may serve as a basis for determining whether a subject with a history of occupational lead exposure has elevated bone lead concentration compared to age and sex adjusted norms.

Preliminary data has been analyzed on three hypertensive black male subjects who have completed the norepinephrine infusion protocol. The first subject was a 52 year old demolition worker with a blood lead concentration of 17.3 μg/dl, the second subject was a 57 year old scrap metal worker with a blood lead concentration of 56.6, and the third subject was a 53 year old machinist with a blood lead concentration of 38.1. In each subject, norepinephrine infusion resulted in a linear increase in blood pressure. After adjustment for the placebo cycle, the mean change in slope relating systolic and diastolic to norepinephrine infusion rate was consistent with a slight chelation induced decline in vascular responsiveness; however, critical assessment of the relationship awaits the analysis of data from additional subjects.

The relationship between K x–ray fluorescence measurement of bone lead concentration and creatinine corrected urinary lead excretion after a single oral dose of DMSA dose has undergone preliminary investigation in 27 subjects, age 22 to 67, with a range of occupational lead exposures. Urine lead concentration after DMSA was significantly correlated with tibia lead concentration ($r = .71$, $p < .0001$), patella lead concentration ($r = .63$, $p < .0001$), and blood lead concentration ($r = .86$, $p < .0001$). Bone lead concentration in this cohort was not significantly correlated with age.

Publications

Kosnett MJ, Becker CE, Osterloh JD, Kelly TJ, Pasta DJ: Factors Influencing Bone Lead Concentration in a Suburban Community Assessed By Noninvasive K X–Ray Fluorescence. JAMA, in press, 1994

Kosnett MJ, North W, Herzberg W, Wu P: Bone Lead Concentration After Delayed Intoxication From Retained Buckshot. Vet Hum Toxicol 35:354, 1993 (Abstract)

Kosnett MJ, Becker CE, Osterloh JD, Kelly TJ: Assessment of Body Lead Burden by K X–ray Fluorescence Measurement of Lead in Bone. Vet Hum Toxicol 34:355, 1992 (Abstract)

Kosnett MJ: Unanswered Questions in Metal Chelation. Clin Toxicol 30:529–547, 1992

Occupational Risks of Pesticide Exposure for Females

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Importance to Occupational Safety and Health

Each year there is an increasing number of females entering the workplace. Women can no longer be discriminated against when applying for a position in which exposure to a hazardous agent is likely. This becomes a great concern when such women are of childbearing age. There is a need to critically evaluate the toxicity of hazardous chemicals on reproductive function of females both prior to and during pregnancy.

Objectives

This study will provide a comprehensive evaluation of the toxic effects of the estrogenic pesticide methoxychlor on the reproductive tract. Exposure of the non–pregnant and the pregnant female will provide the models to evaluate the relative risks of these individuals to impairment of morphological and physiological parameters of the reproductive tract. This study will examine functional outcomes such as effects on fertility and pregnancy and correlate these with the observed anatomic and metabolic alterations within the reproductive tract as measured through the use of biological markers. It is anticipated that critical use of these biomarkers will allow the development of a means of identifying women to be at reproductive risk following exposure to a toxic agent.

Methodology

Adult non–pregnant mice (7–10 weeks old) were exposed to specific doses of the pesticide methoxychlor for five consecutive days/week for four consecutive weeks. Animals were sacrificed either immediately following exposure or allowed to mate in order to ascertain whether the observed toxicity was reversible once exposure ceased. Morphometric measurements of the height of the cells lining the uterine cavity were taken. These endometrial cells were also examined with the electron microscope in order to observe alterations in cellular organelles indicative of alterations in metabolic activity of these cells. Radioimmunoassays were also done to determine circulating estrogen levels in serum following exposure. Additionally, assessments of the fertility of these mice were conducted following the exposure period. In the second part of the study, an evaluation of the effects of methoxychlor on the implantation process was conducted on pregnant mice.

Significant Findings

Non–Pregnant Females

Experiments in which mice were exposed for four weeks to specific doses of methoxychlor revealed a dose–dependent increase in the heights of uterine epithelial cells which line the uterine lumen. Cell heights of the two groups treated with the highest doses of methoxychlor (2.5 and 5.0 mg) were similar to that of the group treated with estradiol–17β. This appears to be an estrogenic response induced by methoxychlor. Electron microscopy revealed increased vacuolization and swelling of mitochondria, dilated rough endoplasmic reticulum and Golgi complexes and fewer microvilli in uterine epithelial cells. These alteration in cellular organelles were not observed in the estradiol–treated group, and thus, appear to be a result of the toxicity of methoxychlor directed toward the uterine lining. Rough endoplasmic reticulum and Golgi complexes are actively engaged in protein synthesis and in packaging of such protein for secretion. Morphologic alterations in these organelles may result in changes in protein secretion within the uterus of methoxychlor–treated mice. It appears that in light of the overall appearance of the cells of the uterine lining and the condition of the organelles in these cells, it is unlikely that such a uterus could accept a fertilized egg for successful implantation. Radioimmunoassay studies performed immediately after a four–week exposure to methoxychlor have revealed increased serum levels of estrogen.

It does appear though that these effects are reversible once exposure ceases. When methoxychlor exposure ceases after four weeks, animals are able to mate, become pregnant and deliver what appear to be normal young. Therefore, even though a constant exposure of an adult results in reproductive toxicity, removal of the individual from the exposure restores the reproductive integrity of the individual.

Pregnant Females

Exposure of pregnant females on Days 4, 5 and 6 of pregnancy to either 5.0 or 10.0 mg methoxychlor resulted in a decrease in survivability of embryos when examined on Day 7, twenty–four hours following the final exposure. Animals exposed to lower doses of methoxychlor (1.25 or 2.5 mg) exhibited no deleterious effects on implanting embryos on the day examined. This time is critical, since implantation is occurring during this period. Whether the uterus is the target site for the action of methoxychlor as reported in the studies with non–pregnant mice or whether the embryo is the target cannot be ascertained as of yet. Histological and histochemical evaluations of these tissues will be performed to confirm the target site and attempt to elucidate the mechanism for this toxic action. What effect such an exposure might have on future pregnancies is not known.

Publications

Swartz WJ, Wink CS, Johnson WD: Response of Adult Murine Uterine Epithelium to 50% Methoxychlor. Reproductive Toxicology, in press, 1994

Swartz WJ, Wink CS, Johnson, WD: Response of Adult Murine Uterine Epithelium to Methoxychlor Exposure. Anatomical Record Suppl., 1:109, 1993 (Abstract)

Swartz WJ, Corkern M: Effects of Methoxychlor Treatment of Pregnant Mice on Female Offspring of the Treated and Subsequent Pregnancies. Reproductive Toxicology 6:431–437, 1992

Martinez EM, Swartz WJ: Effects of Methoxychlor on the Reproductive System of the Adult Female Mouse. II. Ultrastructural Observations. Reproductive Toxicology 6:93–98, 1992

Martinez EM, Swartz WJ: Effects of Methoxychlor on the Reproductive System of the Adult Female Mouse. I. Gross and Histological Observations. Reproductive Toxicology 5:139–147, 1991

Swartz WJ, Corkern M: Reproductive Alterations Induced by Exposure of Mice to Methoxychlor During Pregnancy. Anat Rec, 229:87A, 1991 (Abstract)

Swartz WJ, Mall GM: Chlordecone–Induced Follicular Toxicity in Mouse Ovaries. Reproductive Toxicology 3:203–206, 1989

Martinez EM, Swartz WJ: Response of the Murine Ovary to Methoxychlor Exposure. Anat Rec, 223:75A, 1989 (Abstract)

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

Menstrual Function and Physical and Mental Job Stress

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Program Area: *Disorders of Reproduction*
Grant Number: *5 R01 OH02885-03*
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Importance to Occupational Safety and Health

The menstrual cycle is a marker of female reproductive physiology and can serve to monitor female workers who never attempt or achieve a pregnancy, but whose reproductive function and risk of hormone–related chronic disease may nonetheless be affected by the work environment. This project is investigating menstrual function in women workers, in relation to physical and mental job stress, and stress–related behaviors like caffeine consumption. Both cycle characteristics and ovarian hormone patterns will be studied. Stress is a pervasive occupational exposure and one that potentially can be prevented or reduced. It may be a particular problem for women whose added responsibility for the so–called "second shift" does not readily allow for recovery from job stress during nonwork hours.

Objectives

This project addresses two important issues: (1) job stress in females – an exposure whose effect needs rigorous investigation both on its own merits and to help disentangle stress effects from effects of other workplace agents; and (2) the need to develop biological markers of ovarian function in order to identify and prevent work–related disorders among

nonpregnant women (much as semen analysis has served to monitor male occupational exposures).

Methodology

We have followed 100 female nurses from Memorial Sloan–Kettering Cancer Center (MSKCC) for three consecutive menstrual cycles. Nurses were selected as the target population because previous research has shown them to have high job stress levels. To maximize the range of job stress levels, subjects were recruited from areas of the hospital judged to be "high" and "low" stress on the basis of archival material and discussions with administrators.

Subjects were asked to record basal body temperature, collect a small aliquot of urine daily, and maintain a structured menstrual diary. To evaluate ovulatory and luteal function, urine samples are being analyzed for estrone–3–glucuronide (E_1G), pregnanediol–3–glucuronide (PdG), luteinizing hormone (LH) and creatinine (CR). Salivary samples have been collected for measurement of cortisol, a physiologic indicator of stress.

Using a similar design and translations of our data collection instruments, collaborators in Rome, Italy have conducted an investigation of nurses at the 3,000–bed University hospital.

Significant Findings

Data collection is now complete. Information from the daily diaries has been coded and entered. As hormone assays are still pending, the initial analyses have utilized the diary data on cycle characteristics. Cycle length has been studied in connection with age, self–reported work stress, social support, smoking levels, and caffeine consumption. In general, there was little variability across cycles in the exposures of interest or in cycle characteristics.

The data show the expected relationship between age and cycle length; mean cycle length and variability decrease with increasing age (r=–0.27, p=.0001).

Age (in years)	n (in cycles)	Mean Cycle Length (in days)	Standard Deviation
22–27	47	31.47	8.33
28–33	103	29.44	4.71
34–39	78	27.15	3.37
40–45	57	27.49	2.85
46–52	12	26.67	3.06

Age was also found to be significantly correlated with social support and smoking; younger women smoked more cigarettes on average and received more social support on average than older women (r=–0.11, p= .05, and r=–0.14, p= .02 respectively). As expected, social support was found to be inversely proportionate to stress (r= –0.31, p= .0001).

The data also show a tendency for cycle length to be 2 to 3 days shorter among heavier smokers; however, this trend is based on a small number of heavy smokers (20+ cigarettes per day). Caffeine consumption did not appear to have an appreciable effect on cycle length. Preliminary analyses of job stress and work–related social support also did not show clear and consistent effects on cycle length.

Future analyses incorporating the hormone assay results will complement the data on cycle characteristics.

Publications

X Shu, Brinton L, Zheng W, Swanson C, Hatch M, Gao Y–T, Frauneni J: Relation of Obesity and Body Fat Distribution to Endometrial Cancer in Shanghai, China. Cancer Res, in press, 1992

Hatch M: The Epidemiology of Electric and Magnetic Field Exposures in the Power Frequency Range and Reproductive Outcomes. Paed Peri Epidemiol 6:198–214, 1992

Semen as a Biomarker of Effect Among Lead Exposed Men

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Grant Number: *5 R03 OH02966-02*
Start & End Dates: *04/01/92 – 03/31/94*
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Importance to Occupational Safety and Health

This study will provide information on the reproductive consequences of occupational lead exposure, and will serve as a model for evaluating the effects of occupational and environmental exposures on male reproductive function.

Objectives

The overall objective of this project is to use semen quality as a biomarker of effect on the male reproductive system resulting from occupational and environmental exposures. Occupational exposure to lead will be the focus of this study.

Methodology

The study design is a cross–sectional survey comparing semen quality parameters, serum reproductive hormone levels, and reproductive histories among men occupationally exposed to lead. The men in the study population are workers employed at a large lead–zinc smelter in British Columbia. The workers have blood lead levels ranging from less than 15 μg/dl to greater than 55 μg/dl. Study participants were recruited from the entire male employee population by the means of a postal questionnaire. The questionnaire documents reproductive histories, socio–demographic characteristics, personal habits, such as tobacco and alcohol use, current and past illness, and a range of symptoms potentially related to lead exposure. Of the 2469 male employees contacted (2156 current employees and 340 employees laid–off in 1992) 922 returned questionnaires, 148 provided blood and urine samples; 121 of the latter 148 workers also provided semen samples. Nine repeated semen samples were obtained.

Recent lead exposure was determined by measuring blood lead and zinc protoporphyrin levels. A first A.M. void urine sample was obtained for measurement of urinary porphyrins. Aliquots of blood, urine, and semen were frozen for future analysis for metals other than lead. Information on past lead exposure was obtained from company employment and health records for all individuals who participated in the study. These data include the work histories of all employees and blood lead monitoring data from the worker health program. The exposure assessment will include data on length of employment, work area, job task, and routine blood lead screening values. Summary values were obtained for all currently employed workers to compare the study participants with the non–participants.

Semen samples were collected at home or on site and delivered to the field laboratory within one hour of collection. The semen samples were processed according to standard protocol recording the sperm concentration, count, motility, morphology, and viability. Further analysis was done using computer assisted sperm analysis (CASA) techniques for motility and morphometry. Aliquots of semen were cryopreserved for a flow cytometric assay of sperm chromatin structure and a sperm penetration assay which will be conducted at a later date. Plasma levels of testosterone, follicle stimulating hormone, and luteinizing hormone were measured to evaluate the effect of lead exposure on the hormonal control of the male reproductive system.

The effects of acute and chronic lead exposure on the semen quality parameters and reproductive hormones will be assessed by comparing these measures of reproductive health between subjects with high, moderate, and low lead exposure. Dose–response models will be derived for the various semen quality parameters and reproductive hormones with respect to current and long–term lead exposures.

Significant Findings

None to date.

Reproductive Health of Female Migrant Farm Workers

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Program Area: *Disorders of Reproduction*
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Importance to Occupational Safety and Health

Migrant farmworkers, especially female farmworkers, have been one of the most underserved and understudied occupational populations in the United States. Occupational risks and hazards associated with agricultural work are ranked among the highest in the United States. Among adverse health outcomes due to occupational exposures, adverse reproductive health outcomes among women in the migrant farm labor force have been studied very little. Female farmworkers experience potential occupational hazards, such as prolonged standing and bending when working at conveyor belts or harvesting, long shifts, overexertion, and fatigue, as well as potential exposure to pesticides, climatic extremes, and insufficient toilet facilities in the fields (which may lead to infrequent use of the toilet facilities and thus may in turn result in urinary infections that can lead to adverse reproductive outcomes). In addition, the low socio–economic status, poor access to health care, and migratory lifestyle of these workers, as well as their often undocumented stay, contribute to the fact that high quality data about the health of farmworkers, specifically female farmworkers and their offspring, are almost non–existent.

Objectives

The primary objective of this cross–sectional hypothesis–generating pilot study is to investigate the reproductive health of a sample of minority, largely Hispanic, women (aged 18–45), living in a California farmworker community, and to evaluate and improve study tools and methods for future research purposes for studying adverse effects in this population. The specific aims of this study are: (1) to conduct a survey of women living in a California farmlabor community, using a questionnaire covering demographic and health characteristics, the availability and the use of basic health care for and by the target population, and occupational activities and exposures; (2) to determine and compare the prevalence of gynecologic and reproductive health problems between women who work as farmworkers as compared to women who do not perform such work; (3) to determine the prevalence of specific gynecologic and reproductive health problems in female farmworkers engaged in different specific farmwork activities and compare them to women who are not performing farmwork; (4) to determine the prevalence of pregnancy complications at birth, experienced by the study women and their newborns, to compare the prevalences to those women not engaged in farmwork, and to determine any relationship to specific occupational farmwork activities; (5) to review and refine the study design, study instruments, and community approach for future studies in farmworker communities in different agricultural regions of California and other states.

Methodology

A pilot study has been carried out, as a necessary step to characterize the population, to develop acceptable and appropriate approaches for community cooperation, to develop the correct sampling methodology, to determine the community response and learn about the bi–cultural setting, all of which will ultimately aid the researchers in developing the most accurate, acceptable and comprehensible bilingual, bicultural approach.

Parlier, an agricultural community in Fresno county, California, was chosen to serve as the target community for the pilot study. Once chosen, the area, which encompassed the zip code district of Parlier, was divided into enumeration parcels, including both urban and rural areas. After random sampling of several enumeration blocks, the dwelling units on each block were mapped out for each parcel of land for later enumeration of the target population. From each sampled and mapped block, dwellings were randomly chosen and their occupants enumerated for further interviewing purposes. After the enumeration, female occupants were randomly sampled, and an extensive interview using a pretested questionnaire was administered by bicultural, bilingual interviewers in the homes of respondents. After the interviews were administered and reviewed for completeness, the answers were coded and entered into a computerized data base. In addition, limited physical examinations of participants were conducted in the community clinic to determine weight, height, pulmonary function, as well as limited blood tests to assess hematocrit and other hematologic values, and urinalysis. Each study participant who

completed both the questionnaire and the limited physical exam was monetarily compensated ($20/participant).

Statistical data analyses of the interview–based and the lab–based findings are now being performed and are nearing completion. The analysis is focusing on the association of reproductive health outcomes with exposure to farming activities. Women not employed as farmworkers will serve as the comparison group. Specific outcome variables of interest are menstrual cycle irregularities, pregnancy and birth complications, as well as spontaneous abortions. The final results of the pilot study will be used to plan and implement a full–scale study in several agricultural regions of California, which is planned to begin in spring of 1994.

Significant Findings

In the community–based pilot study in Parlier, 60 women, aged 18 to 44 years (a subsample of 150 adults interviewed), were enrolled to participate in a cross–sectional assessment of reproductive and gynecological health outcomes among others. The response rate was fairly high (75%) for this population which works long hours and lives in crowded conditions. Preliminary results show that: more than 90% of the women were of Hispanic origin, 67% were born in Mexico; 83% were married or living as married; 91% had at some point performed agricultural work, and 65% had worked in agriculture the previous year; 31% described themselves migrant farmworkers, and 18% moved for work purposes. In terms of reproductive outcomes: 80% had been pregnant (n=48); the miscarriage rate per pregnancy was 11% and low birth weight rate 7% (both of which are comparable to general population rates); the pregnancy and delivery complication rate, however, was 34% and the premature labor rate was 10%.

Occupational Neuropathies Due to Industrial Chemicals

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Importance to Occupational Safety and Health

Occupational exposure to one or multiple chemicals may cause neuropathies. Studies in this project are aimed to develop methods for screening or monitoring biological workers for over-exposure to neurotoxicants. The industrial solvents n-hexane and carbon disulfide (CS_2) were selected because of their potential to produce neurotoxicity and the potential for occupational exposure. Assay of biomarkers for exposure to chemicals can improve the assessment of exposure, dose-response, and comparison of dose between species. Such studies in experimental animals using defined exposures to neurotoxic chemicals can assist in the interpretation of neurological disorders in workers.

Objectives

The overall objective of this project is the prevention of occupational neurodegenerative disorders following exposure to industrial chemicals. Biological markers will be developed for early detection of exposure to n-hexane/metabolites and CS_2.

Methodology

The principle in developing biomarkers for exposure to n-hexane and CS_2 is based on the reactivity of the n-hexane metabolite, 2,5-hexanedione (2,5-HD), and CS_2 that allows them to react with specific proteins in the body, thus providing a long-term dosimeter. 2,5-HD reacts with amino groups of lysine residues to form protein-bound pyrroles. CS_2 reacts with lysyl amino groups to yield dithicarbamates. We have developed monoclonal and polyclonal antibodies to bovine serum albumin (BSA)-pyrrole derivative of 2,5-HD. Studies on antibodies for BSA-bound CS_2 have started. We have demonstrated that serum protein-bound pyrroles are not suitable biomarkers for 2,5-HD since they may undergo autoxidation resulting in crosslinked proteins that do not react with the protein-pyrrole antibodies following exposure to 2,5-HD. Furthermore, the rapid turnover of the circulating serum proteins might result in the replacement of modified proteins, leading to a decreased titer so that they may not be detected. This is consistent with our results that neither monoclonal nor polyclonal antibodies reacted with serum from 2,5-HD-treated rats. In contrast, antibodies against BSA-pyrrole derivatives gave positive reactions with hair protein-bound pyrroles from 2,5-HD treated rats. Our preliminary results indicated that polyclonal antibodies to BSA-pyrrole derivative of 2,5-HD reacted positively with protein-bound pyrrole compounds, both in the intact hair and in the solubilized hair of 2,5-HD-treated rats. Similar studies are being conducted on CS_2. In addition, we have been studying 2,5-HD pyrrole derivatives in the urine as a biomarker for 2,5-HD and n-hexane-treated rats. We plan to develop biomarkers for n-hexane/metabolites and CS_2 to provide a means of assessing exposure to these chemicals and of comparing internal dose between species including man, resulting from short- to long-term exposure, and from low- to high-dose.

Significant Findings

During the initial phase of this project, we have established the following two important findings: (1) protein-pyrrole derivatives of 2,5-HD in blood are not suitable markers for detecting exposure to 2,5-HD since they may undergo autoxidation and crosslinking that drastically change their immunoreactivity to monoclonal and polyclonal antibodies for protein pyrroles, (2) the finding of hair protein-bound pyrroles, which can act as sensitive and accurate biomarkers for exposure to n-hexane and metabolites. Furthermore, the protein-bound pyrrole derivatives formed in the hair are time-dependent and their longitudinal accumulation a reflection of the duration and level of exposure to n-hexane/metabolite. This would make the hair an accurate dosimeter that would give a good approximation of the duration and level of exposure. A significant advantage of the proposed studies is that hair protein-bound chemicals can be detected and quantified in early preneurotoxic conditions and correlated with subsequent neurologic deficits to determine their temporal relationship to development of neurotoxicity. We plan to carry out these studies on rats exposed via inhalation to n-hexane or oral administration or injection of 2,5-HD. Similar studies will be carried out following inhalation of

CS_2. Since the neurotoxicity of both n–hexane and CS_2 is increased with concurrent exposure to methyl isobutyl ketone (MiBK), a situation that occurs in some occupational environments, we plan to carry out studies on the effect of simultaneous exposure to MiBK in the formation of these biomarkers. Correlations will be made between these biomarkers and kinase activity in red blood cells and in nervous tissues. Protein–bound pyrroles will be investigated as biomarkers in human hair transplants in the nude mouse. Integration with other results will be essential for human hazard identification and exposure response characterization.

Publications

Lanning CL, Wilmarth KR, Abou–Donia MB: *In Vitro* Binding of 2,5[^{14}C]hexanedione to Cytoskeletal Proteins. Neurochem Int, in press, 1994

Jensen KF, Wilmarth KR, Olin JK, Abou–Donia MB: Immunohistochemical Characterization of Carbon Disulfide (CS_2) Induced Cytoskeletal Alterations in the Central Nervous System. Toxicologist, 1994 (Abstract)

Wilmarth KR, Viana ME, Abou–Donia MB: Evidence for Crosslinking of Neurofilament (NF) Proteins in Rat Spinal Cord Following Inhalation Exposed to Carbon Disulfide (CS_2). Toxicologist, 1994 (Abstract)

Johnson DJ, Lack L, Abdel–Rahman SM, Abou–Donia MB: Hair as a Target Tissue for Protein Binding Following Subchronic Intraperitoneal Injection of 2,5–Hexanedione. Toxicologist, 1994 (Abstract)

Wilmarth KR, Viana ME, Abou–Donia MB: Carbon Disulfide Inhalation Increases Ca^{2+}/Calmodulin–dependent Kinase Phosphorylation of Cytoskeletal Proteins in the Rat Central Nervous System. Brain Res 628:293–300, 1993

Johnson DJ, Lack L, Abou–Donia MB: Hair As A Target Tissue for Developing A Biological Marker for Precursors to 2,5–hexanedione. IN: Biomarkers of Human Exposure to Pesticides, (eds. MA Saleh, JN Blancato, CH Nauman), American Chemical Society, Washington, DC, pp. 125–132, 1993

Knoth–Anderson J, Veronesi B, Jones K, Lapadula DM, Abou–Donia MB: Triphenyl Phosphite–induced Ultrastructural Changes in Bovine Adrenomedullary Chromaffin Cells. Toxicol Appl Pharmacol 112:110–119, 1992

Anderson JK, Abou–Donia MB: Adrenomedullary Chromaffin Cells: A Well Characterized Model System for Toxicological Studies. In: *In Vitro* Biological Models, (eds. Tyson and Frazier), Academic Press, (Vol 1 of Methods in Toxicology), San Diego, CA, 1992

Abou–Donia MB: Triphenyl Phosphite: A Type II Organophosphorus Compound Induced Neurotoxic Agent. In: Organophosphate: Chemistry, Fate, Effects. (eds. J Chambers, PE Levi), Academic Press, San Diego CA, 327–351, 1992

Abou–Donia MB, Hu Z, Lapadula DM, Gupta RP: Mechanisms of Joint Neurotoxicity of n–hexane, Methyl Isobutyl Ketone, and O–ethyl O–4–nitrophenyl Phenylphosphonothioate (EPN) in Hens. J Pharmacol Exper Thera 257:282–289, 1991

Lapadula DM, Habig C, Gupta RP, Abou–Donia MB: Induction of Cytochrome P–450 Isozymes by Simultaneous Inhalation Exposure of Hens to n–hexane and Methyl Iso–butyl Ketone (MiBK). Biochem Pharmacol 41:877–883, 1991

Somkuti SG, Lapadula DM, Chapin RE, Abou–Donia MB: Light and Electron Microscopic Evidence of Tri–o–cresyl Phosphate (TOCP)–mediated Testicular Toxicity in Fischer 344 Rats. Toxicol Appl Pharmacol 107:35–46, 1991

Gupta RP, Lapadula DM, Abou–Donia MB: Purification and Characterization of Cytochrome P–450 Isozymes from Phenobarbital–induced Adult 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–naphthoflavone–induced Hen Liver. Arch Biochem Biophys 282:170–182, 1990

Abou–Donia MB, Nomeir AA, Bower JH, Makkawy HA: Absorption, Distribution, Excretion, and Metabolism of A Single Oral Dose of [14C]Tri–o–cresyl Phosphate (TOCP) in the Male Rat. Toxicology 65:61–74, 1990

Somkuti SG, Abou–Donia MB: Disposition, Elimination, and Metabolism of Tri–o–Cresyl Phosphate Following Daily Oral Administration in Fischer 344 Male Rats. Arch Toxicol 64:572–579, 1990

Abou–Donia MB, Suwita E, Nomeir A: Absorption, Distribution, and Elimination of A Single Oral Dose

of [14C]Tri–o–cresyl Phosphate in Hen. Toxicology 61:13–25, 1990

Suwita E, Abou–Donia MB: Pharmacokinetics and Metabolism of A Single Neurotoxic Oral Dose of Tri–o–cresyl Phosphate in Hens. Arch Toxicol 64:237–241, 1990

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

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

Abou–Donia MB, Lapadula DM: Studies on the Molecular 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

Carrington CD, Abou–Donia MB: Triphenyl Phosphite Neurotoxicity in the Hen: Inhibition of Neurotoxic Esterase and Prophylaxis by Phenylmethylsufonyl Fluoride. Arch Toxicol 62:375–380, 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

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–Q–Cresyl Phosphate Treatment in Male Fischer 344 Rats: Biochemical, Neurobehavioral, and Neuropathological Studies. Fund Appl Toxicol 199–205, 1988

Somkuti SG, Lapadula RE, Chapin JC, Lamb IV, Abou–Donia MB: Reproductive Tract Lesions Resulting from Subchronic Administration (63) days of Tri–o–cresyl Phosphate in Male Rats. Toxicol Appl Pharmacol 89:49–63, 1987

Somkuti SG, Lapadula RE, Chapin JC, Lamb IV, Abou–Donia MB: Time Course of the Tri–o–cresyl Phosphate–induced Testicular Lesion in F–344 Rats: Enzymatic, Hormonal, and Sperm Parameter Studies. Toxicol Appl Pharmacol 89:64–72, 1987

Somkuti SG, Lapadula RE, Chapin JC, Lamb IV, Abou–Donia MB: Testicular Toxicity Following Oral Administration of Tri–o–cresyl Phosphate (TOCP) in Roosters. Toxicol Lett 37:279–290, 1987

Suwita E, Nomeir AA, Abou–Donia MB: Disposition, Pharmacokinetics, and Metabolism of a Dermal Dose of [^{14}C] 2,5–Hexanedione in Hens. Drug Metab Disp 15:779–785, 1987

Lapadula DM, Tilson HA, Campbell G, Abou–Donia MB: Neurotoxic Effects of Combined Treatment of 2,5–Hexanedione and Trithyllead Chloride. J Toxicol Environ Health 21:483–492, 1987

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

Abou–Donia MK, Makkawy HM, Campbell GM: The Pattern of Neurotoxicity Produced by Dermal Application of n–hexane, Methyl n–butyl Ketone, 2,5–hexanediol, and 2,5–hexanedione Alone and In Combination with O–ethyl O–4–nitrophenyl Phenylphosphonothioate in Hens. J Toxicol Environ Health 16:85–100, 1985

Nomeir AA, Abou–Donia MB: Analysis of n–hexane, 2–hexanone, and 2,5–hexabedione, and

Related Chemicals by Capillary Gas Chromatography and High–Pressure Liquid Chromatography. Anal Biochem 151:381–388, 1985

Neurologic Effects of Solvents and Age in Older Adults

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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 that 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 working years may therefore be at increased risk for significant neurologic problems attributable to their former work, even though such problems may have been inapparent during the periods of solvent exposure.

Objectives

The study addressed the following questions:

1. Are there decrements in neurologic function among the retired painters relative to the control population?
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. Secondarily, are there intergroup differences among selected non–neurologic areas of function?

Methodology

The study used a cross–sectional design to examine neurologic function (subjective, neurosensory, neuropsychological, and psychiatric parameters) among 89 retired, formerly solvent–exposed workers (67 Painters; 22 Aerospace painters and fuel cell sealers) in comparison to 126 retired Carpenters, who had relatively minimal prior occupational solvent exposures. Neurologic function was also evaluated relative to semiquantitative indices of recalled past solvent exposure. Non–neurologic parameters, including respiratory symptoms, spirometry, blood tests of liver function, and urine proteins were also examined as outcomes of secondary interest.

Subjects were identified systematically through pension funds. The proportions of invited retirees who responded to approach materials (47–52%) and who were willing and eligible to participate (25–31%) were relatively low but uniform across the study groups. Surveys of non–respondent retirees in each study group revealed similar distributions of reasons for non–response. By design, all subjects were male, with ages 62–74 years and at least 1 year since retirement (average 5 years). The exposed subjects on average had 25–30 years experience in solvent–exposed occupations.

Significant Findings

Lifetime cumulative alcohol use was 1.5–2.5 times greater among current and former drinkers, respectively, for Painters in comparison to Carpenters and Aerospace Workers. It is plausible that the history of heavier alcohol consumption in Painters represents a direct or indirect consequence of solvent exposure, as speculated previously in other reports. However, this is not supported by the absence of such a pattern in the Aerospace Workers.

The Aerospace Workers showed significantly worse mean performance on neuropsychological tests of memory and visual–motor speed, and to lesser degree motor and attention/concentration abilities. The total number of individual tests on which Aerospace Workers scored worse than 90% of Carpenters ("total outlier number") was more commonly relatively "high" compared to the Carpenters; however, their *highest* total outlier numbers were still lower than the Carpenters' worst 90th percentile value. This suggests that this

probable solvent effect is singularly of less magnitude than contributory factors unrelated to solvents.

Among the (non–aerospace) Painters, neurologic and depressive symptoms were significantly more common than either Carpenters or Aerospace Workers. However, even with lower mean vocabulary test scores and higher cumulative alcohol consumption, the (non–aerospace) Painters showed little evidence of relative dysfunction on neuropsychological testing. Neurosensory testing (vibratory tactile perception and color visual discrimination abilities) showed no clear evidence of relative dysfunction possibly attributable to prior solvent exposure, in either Painters or Aerospace Workers. The absence of such findings on neuropsychological testing of Painters and on neurosensory testing of both exposed groups stands in strong contrast to (and calls into question the long–term clinical relevance of) the repeatedly positive findings in multiple previous studies of pre–retirement workers with similar occupational exposures.

The average, cumulative and era–specific solvent exposure indices in numeric form showed no significant association with any major outcome variables. However, when exposed subjects were categorized into index tertiles, the Aerospace Workers with relatively moderate or high cumulative solvent exposure showed greatest evidence of adverse association between exposure and neuropsychological test performance. There was also no evidence that temporal phenomena, such as latency or recency, were involved in the observed associations between prior solvent exposure and neuropsychological test performance. There were no significant associations between test performance and either solvent–alcohol or solvent–age interactive terms (within the narrow sample age range), beyond those observed for the individual variables.

The Painters, but not the Aerospace Workers, showed increased risk for possible restrictive ventilatory dysfunction (by spirometry), consistent with probable long–term adverse pulmonary effects of occupational exposures, speculatively either paint or asbestos exposures.

There were no significant differences on liver function tests or on urinary excretion of total protein or NAG enzyme, providing no evidence of persistent effect by long–term solvent exposure on liver or renal excretory function.

Central Nervous System Effects of PCE Exposure in Humans

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Importance to Occupational Safety and Health

This study examines for the first time the relationship between chronic exposure to perchloroethylene (PCE) and the prevalence of symptoms, neurobehavior, and neurophysiologic central nervous system (CNS) effects in workers. These effects are being evaluated in dry cleaners occupationally exposed to different levels of PCE using never–exposed laundry workers as a reference population. 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 completion of the study, the prevalence of chronic CNS effects will be thoroughly characterized between 0 and 100 ppm, and the lower threshold of adverse symptoms, behavior, and physiologic effects will be known at the 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. The behavioral hypothesis posits that functions such as the ability to alternate between tasks and other tests requiring integration of complex attention and visuo–spatial skills, primarily frontal lobe functions, should be more affected by exposure to PCE. In contrast, simple attention, motor speed, and verbal ability should be affected by PCE exposure to a lesser extent. In addition, solvent exposures are known to affect memory and mood, associated with the limbic system.

Methodology

The cross–sectional CNS evaluation is being conducted on 84 never–exposed laundry workers,

42 low, 42 moderate, and 84 highly exposed dry cleaner employees in the Western Washington area. To control for acute exposure effects, the symptom and behavioral evaluations are conducted over 3 sessions; on the afternoon of their day off; 36 hours post–exposure in the morning at their work site, and again after the workshift. The core behavioral battery is presented in Table 1. A pre– and post–exposure alveolar breath sample is measured to control for variation in PCE body burden, supplementing 8 hr air monitoring for each exposed and for one out of eight non–exposed workers. Exposure zones will be based on (1) distance form PCE source, (2) PCE air levels, (3) PCE breath levels. Full–shift continuous PCE peak sampling (Bruel and Kjaer 1302) is being conducted on operators with fluctuating exposures. These exposure measures are used to construct lifetime indices of cumulative exposure. The 2–hour neurophysiologic assessment occurs at least 24 hours post–exposure on a separate day. Paid volunteers must have at least 1 year on the job, are older than 18 years old, english speaking, and have had no history of CNS disorders. No subjects will be excluded on the basis of alcohol or drug 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 stop, 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.

The analysis will be conducted in two phases. First, within each separate category of health outcomes, efforts will be made to identify reliable measures. Two methods will be compared to reduce the number of variables resulting in a set of more reliable and uncorrelated composite variables. The first way is to group variables into clinically consistent categories. This approach is to be compared with a principal factor analysis (RxT). The same factor analysis will be repeated for the zero, low, moderate, high, and previously exposed PCE exposure categories, identifying the number of underlying dimensions corresponding to the hypothesis. The analysis of an *a priori* hypothesis eliminates the concern cumulative alpha error being responsible for positive results. The difference in relationships between symptoms, neurobehavior, and physiological measures will be examined for zero, low, moderate, and high acute and chronic exposure categories. The CNS data would be reanalyzed using these factors as new outcome variables in regression models to increase the statistical strength of the exposure–effect relationship. The second step is to model the potential exposure–effect relationships.

Table 1. The Test Battery

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	Wisconsin card sort	P
Memory			
Short Term:	VS	Pattern Memory	C
	VS	Pattern Recognition	C
	VS	Visual Reproduction	P
	VB	Cal Verb Learn Test	P
Mood	VS	POMS	P
	VB	POMS	P
Basic Skill	VS	Vocab	C
	VS	Arith	C
Add ons	VS	Switch	C
	VS	, Color Hue	P

C = Computerized
MD = Manual Dexterity
P = Paper and Pencil
VB = Verbal
VS = Visual

Significant Findings

Data collection and analysis is in progress. However a preliminary study evaluating how to interpret the ability to switch between tasks, the L'Anthony Color Hue Test, and the Stroop Test has been completed. Unexposed production workers at two facilities (n=104), between the ages of 18 and 70 were stratified into 5 age groups and tested pre– and post–shift. The effect of age, sex, repetition, and when possible ethanol consumption, was assessed to establish their use in chronic and acute solvent studies and to estimate psychometric properties. Performance on all tests was affected by age. Repetition improved performance on the switching task and the Stroop Test, but not the Color Hue Test. Ethanol consumption significantly affected the ability to switch, but was examined for the other two tests. Gender did not affect performance. The switching task and the Color Hue Test were added to the core behavioral battery.

Exposure to PCE in commercial shops were quantified by 8 hour time weighted average personal dosimetry, real time area sampling indicating peak exposures, and the amount of PCE in alveolar breath. As expected there was a statistically significant association between all measures. Analysis of variance determined that the type of process and job title were associated with each measure of exposure. The personal badge samples accounted for .88 of the

variance in breath whereas the area samples only accounted for .84 of the total variance. Peak exposures were experienced by wet transfer operators 15% of the time above 50 ppm whereas dry–to–dry operators were exposed to this level less than 1% of their shift. Lastly wet–transfer operations ranged between .2 to 86 ppm.

Publications

Echeverria D, Heyer N, Toutonghi G, Ronhovde N, Bittner A: The Stroop Test: The Effect of Age, Sex, and Color Confusion on Selective Attention Among Unexposed Workers. Advances in Industrial Ergonomics and Safety IV, 1992

Ronhovde N, Heyer N, Toutonghi G, Echeverria D: Color Hue Impairment as An Indicator of CNS function. Advances in Industrial Ergonomics and Safety IV, 1992

Toutonghi G, Echeverria D, Bittner A, Ronhovde N: The Use of Switching Ability to Assess Central Nervous System Function. Advances in Industrial Ergonomic and Safety III, 1991

Ronhovde N, Heyer N, Toutonghi G, Echeverria D: The Effect of Age on Color Vision. Advances in Ergonomics and Safety III, Elsevier, Denver, CO, 1991

Echeverria D, Heyer N, Ronhovde N, Toutonghi G: The Effect of Adverse Color Vision of the Stroop Test. Advances in Ergonomics and Safety III, Elsevier, Denver, CO, 1991

Validity of Computerized Tests in Occupational Settings

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Importance to Occupational Safety and Health

This study represents an attempt to validate a computerized neurobehavioral test battery which can then be used in research studies to investigate CNS dysfunction secondary to neurotoxicant exposure in a valid and theoretically meaningful way. If the battery proves valid as an indicator of CNS function, it will also have utility in clinical examination of patients with suspected encephalopathy secondary to exposure.

Objectives

To examine the relationship between specific types of brain damage (white matter lesions in multiple sclerosis, basal ganglia dysfunction in Parkinson's disease, focal cortical lesions in stroke) and performance on Neurobehavioral Evaluation System (NES) tests.

Methodology

Subjects from each of three neurological groups will be tested with the NES battery and compared to age– and gender–matched controls. The neurological groups include multiple sclerosis, early Parkinson's disease, and focal stroke (the 4 stroke subgroups include left and right anterior, left and right posterior).

Significant Findings

As of 11/23/93, 226 subjects have been tested. Subgroups of patients enlisted were Parkinson's Disease (PD; N=68), multiple sclerosis (MS; N=60), focal lesion (FL; N=31) and normal controls (NC; N=67). We have confirmed that most neurologic patients meeting the exclusion criteria used in the study can complete all of the tests in the battery and that the remainder can complete the majority of tests.

A preliminary analysis of results has been carried out for the PD, MS, and NC groups. Correlations between NES tests were estimated for each of the three groups separately. These correlations were generally small in magnitude, suggesting that the battery taps distinct functions in addition to functions common to the several tests. This held for the neurological patient groups as well as for the controls, indicating sensitivity of these tasks to specific deficits rather than merely to degree of overall impairment.

Linear regression models were fit to the data to estimate associations between disease and test performance, adjusting for differences in age, gender, educational level, and a measure of native cognitive ability. The two disease groups differed from controls in distinct ways. For the PD sample there was an association between disease and tests of motor

speed, hand–eye coordination, visual memory, and a measure of fatigue, all of which had been predicted. In the MS group, significant associations with disease were more widespread. MS patients were impaired on tasks assessing motor speed, hand–eye coordination, psychomotor speed, attention, concentration, verbal memory, visual discrimination, and visual memory. These patients also reported more fatigue than did controls. The contrast between the two disease groups suggests that the present NES battery is more sensitive to the neuropathological consequences of MS (especially white matter lesions) than to those of PD (dysfunction of the basal ganglia, especially the substantia nigra).

The results indicate that the NES subtests are most effective in measuring the expected motor deficits in PD and MS. However, they failed to detect deficits in complex attention, visuospatial function, and verbal encoding in PD patients, and deficits in verbal functioning and memory in MS patients, which have been identified in past studies using traditional neuropsychological tests. These limitations have suggested that if the NES is to be effective in detecting CNS dysfunction (especially at the subclinical levels to be expected in working populations exposed to neurotoxicants) the battery requires expansion and further validation.

A Computerized Tool to Screen Workers for Neurotoxicity

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Importance to Occupational Safety and Health

Exposure to chemicals that can cause effects on the nervous system is common, and neurotoxic disorders are one of NIOSH's 10 leading diseases and injuries. Many epidemiologic studies of workers have demonstrated neurobehavioral effects of chemical exposures. However, screening of individuals for early signs of neurotoxicity from workplace exposures is currently rarely performed. Screening of individuals is rare due to the cost of full–scale clinical neuropsychological testing (averaging over $700 per patient nationally), the limited availability of qualified personnel, and the absence of efficient screening tools. Currently available neurobehavioral instruments are optimized for efficient collection of epidemiologic outcome information on groups of workers, not for screening of individuals among exposed workers who may require follow–up examinations.

The present project concerns the first phase of a two–phase effort, development of the new computer–based testing instrument. Successful completion of the proposed project work will lead to the second phase of the overall research program, which includes: (1) assembling a network of clinics to use the neurobehavioral screening system, (2) performing a normative data collection project, and (3) performing a validation study. The system could be adapted to allow its effective use in other countries and in populations potentially most susceptible to effects of neurotoxic exposure such as the elderly and children.

Objectives

The main goal of this effort is to produce a new computer–based neurobehavioral testing system to screen workers for early signs of occupational neurotoxicity. The results of this screening test would provide information to help decide whether individual workers exposed to potential neurotoxicants should be referred for more expensive full–scale clinical neuropsychological assessment. This tool is intended for widespread use in clinics and workplaces. The aims of the present project are to create a set of computer–based neurobehavioral tests specifically for screening of individuals exposed to potentially neurotoxic agents, to pilot test the instrument for feasibility of use, to develop training materials to instruct potential users of the computer–based testing system, and to evaluate those training materials.

Methodology

The project employs new hardware and software technology to accomplish these aims. A pen–based notebook computer with a speech production device is employed. This hardware represents improvements over that used by existing computer–based batteries by allowing both auditory presentation of the tests and recording of responses in a manner equivalent to paper–and–pencil neuropsychological tests. The set of tests to be implemented in this project includes tests of a range of behavioral functions: orientation, verbal learning, spatial memory, visual and cognitive tracking. The screening instrument is to be pilot tested for feasibility of use among 50 outpatients at

an occupational medicine clinic. In addition, training materials are to be developed to instruct potential users of the computer–based testing system. Multi–media capabilities of the hardware/software development environment will be utilized to develop the training materials. A pilot test of these training materials using students in an occupational and environmental health training program will be performed.

Significant Findings

None to date.

Organophosphate Neuropathy and Biomarkers of Exposure

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Importance to Occupational Safety and Health

Poisoning with methamidophos and certain other organophosphate insecticides, including chlorpyrifos, has been reported to cause neuropathy. Recent studies suggest that mild and subclinical neuropathy may affect over 25% of all individuals poisoned with methamidophos, an insecticide used widely by hundreds of thousands of farmers throughout the world. Experimental studies suggest that inhibition of the activity of neuropathy target esterase, which can be measured in lymphocytes, is predictive of subsequent neuropathy and that autoantibodies to neurofilament triplet protein are increased in serum of animals with experimentally induced organophosphate induced neuropathy. We propose to validate these assays among a poisoned population. These assays are potentially of use for screening workers exposed to organophosphate neurotoxins, for predicting the clinical sequela among individuals poisoned with methamidophos, chlorpyrifos, and other organophosphate neurotoxins, and as the basis for further exploration of the mechanism of organophosphate neuropathy.

Objectives

The biological hypothesis under study is that there exists a syndrome of persistent subclinical peripheral neuropathy caused by methamidophos or chlorpyrifos, and that this syndrome can be reliably detected by electrophysiologic assessment of sensory and motor function coupled with assessment of serum autoantibodies to nervous system tissue and assessment of exposure through measurement of NTE activity in circulating lymphocytes.

Specific Aims are:

1. Whether inhibition of lymphocyte neuropathy target esterase (NTE) measured in peripheral lymphocytes is a sensitive and specific index of peripheral neurotoxicity and of serum autoantibodies to peripheral nervous system proteins.
2. Whether previous poisoning with methamidophos or chlorpyrifos results in diminished motor and sensory function, as reflected in electrophysiologic studies, pinch strength, and elevated vibrotactile threshold.
3. Whether a dose–response relationship exists between lymphocyte NTE inhibition and motor or sensory function, or serum autoantibodies.
4. Whether there exist threshold levels of methamidophos or chlorpyrifos exposure, below which either sensory or motor neuropathy is no longer evident.

Methodology

The study population consists of 50 patients previously poisoned with neuropathic organophosphates and treated at two teaching hospitals in Nicaragua plus two control groups: (1) patients poisoned with other organophosphates not known to be neurotoxins, and (2) unexposed cattle rancher controls. At the time of acute poisoning, inhibition of neuropathy target esterase (NTE), the putative target enzyme for organophosphate neuropathy, and serum autoantibodies to neurofilament triplet proteins, are measured in peripheral lymphocytes. Severity of poisoning also is evaluated clinically. Before hospital discharge (and before neuropathy is likely to have occurred), vibrotactile threshold, thermal sensory threshold, dynamometric grip and pinch strength, nerve conduction studies, and clinical evaluations are conducted among poisoned and never poisoned patients (cattle rancher controls). Exposure is characterized by patient interview and field visit to the site of poisoning, and by analysis of residue in dermal wipe samples or in field samples, where necessary, to confirm the pesticide responsible for

poisoning. All patients are re–examined 6 weeks to 3 months after poisoning, long enough for peripheral neuropathy to develop. Convalescent autoantibodies are measured, and baseline neuropathy target esterase is measured at the time of followup. Neuropathy target esterase will be validated against clinical outcome and serum autoantibodies, and dose–response relationships and possible thresholds of inhibition of NTE, necessary for the development of neuropathy, will be examined by measuring acute and subsequent baseline (percent depression) of neuropathy target esterase. All workers will be re–examined two years after poisoning to evaluate the persistence of neuropathy.

Significant Findings

Of the thirty–five acutely poisoned patients recruited to date to this cohort, twenty have been poisoned with the peripheral neurotoxins chlorpyrifos or methamidophos. All thirty–five poisoned patients have been re–examined between 6 weeks and 3 months. In addition, 12 not poisoned cattle ranchers have had two examinations at similar intervals to the controls. In the poisoned cohort, we have identified one case of profound neuropathy who had markedly depressed neuropathy target esterase at the time of acute poisoning.

Publications

McConnell R, Keifer M, Rosenstock L: Elevated Quantitative Vibrotactile Threshold Among Workers Previously Poisoned With Methamidophos and Other Organophosphate Pesticides. Am J of Indust Med, in press, 1993

Neurological Effects of Organophosphates on Farmworkers

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Importance to Occupational Safety and Health

The World Health Organization (WHO) estimates that 600 million people world wide are exposed to pesticides on a regular basis, much of this exposure is to organophosphate pesticides (OP). Past studies have documented persistent neurological effects in previously OP poisoned workers and some with chronic OP exposure. This study will focus on identifying persistent neurobehavioral deficits which may result from chronic long–term pesticide exposure. The results of this study will have direct bearing on the occupational health of the approximately 5 million people in the U.S. who derive some part of their income from agricultural work. The results will also have bearing on the pesticide application industry as structural pesticide applicators use many of the same products.

Objectives

The goal of this clinical epidemiological study is to determine whether farmworkers chronically exposed to OP pesticides in field work have quantifiable nervous system abnormalities after an exposure season and whether these changes are persistent after a several month period of non–exposure.

Methodology

This cross–sectional study with a follow–up component will compare 60 female orchard farm workers with chronic low–level OP exposure to age, education, and language matched unexposed referents. Exposure estimates will be based on orchard spray logs, work questionnaires of subjects, and biological monitoring (cholinesterase testing). A neurological battery including the WHO Neurobehavioral Core Test Battery, vibratory threshold, color discrimination testing, nerve conduction and repetitive stimulation studies, and pattern reversal visual evoked potentials will be applied to both groups, both at the end of an exposure season and again following a 5–6 month period of non–exposure. Several biological markers which may serve as markers of susceptibility, physiological effect, or dose will also be evaluated: cholinesterase, paraoxonase, chlorpyrifos oxonase levels, and muscarinic receptor density in lymphocytes.

Significant Findings

None to date.

The Effects of Impulse Noise on the Auditory System

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Program Area: *Noise-Induced Hearing Loss*
Grant Number: *5 R01 OH01152-12*
Start & End Dates: *07/01/80 – 03/31/96*
Funding Level: *$233,677 ($1,840,031 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 anatomical and physiological changes in the inner ear following traumatic exposures; and (3) to explore the possibility that "toughening" exposures to non–traumatic noise can reduce the amount of hearing loss from a dangerous noise exposure.

Methodology

An electrical–mechanical system is used to produce realistic noise impacts. The hearing of the experimental animals tested, is before and after exposure for twenty 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 Electron Microscopy, 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) In the last few years we have shown that certain low level exposures protect the auditory system from future higher level exposures. During the last year we have found that these prophylactic exposures are effective in reducing the hearing loss produced by high level impact and impulse noise. All of these results have direct implications for the management of workers in noisy environments.

Publications

Subramaniam M, Salvi RJ, Spongr V, Henderson D, Powers NL: Changes in Distortion Product Otoacoustic Emissions and Outer Hair Cells Following Interrupted Noise Exposures. Hearing Research, in press, 1993

Salvi RJ, Henderson D, Clock AE: Effects of Noise Exposure on the Auditory System. In: Handbook of Neurotoxicology Vol. 2, Effects of Mechanisms, (eds. L Chang, R Dyer), Marcell Decker Inc., New York, in press, 1993

Henderson D, Salvi RJ, Boettcher FA, Clock AE: Neurophysiological Correlates of Sensorineural Hearing Loss. Handbook of Clinical Audiology, 4th Edition (ed. J Katz), in press, 1993

Salvi RJ, Henderson D, Clock AE: Effects of Noise Exposure on the Auditory System. In: Handbook of Neurotoxicology Vol 2: Effects and Mechanisms (eds. L Chang, R Dyer), in press, 1993

Subramaniam M, Henderson D, Spongr V: Protection from Noise Induced Hearing Loss: Is Prolonged "Conditioning" Necessary? Hearing Research 65:234–239, 1993

Henderson D, Subramaniam M, Boettcher F: Individual Susceptibility to Noise Induced Hearing Loss: An Old Topic Revisited. Ear and Hearing 14:152–168, 1993

Subramaniam M, Henderson D, Campo P, Spongr V: The Effect of Low Frequency Conditioning on Hearing Loss from High Frequency Noise. J Acoust Soc Am 93:952–956, 1992

Henderson D, Mills J, Colletti V: Psychophysical Limits of Auditory Performance: Implications for the Diagnosis of Hearing Loss. Otolaryngology (ed. M Paparella), Saunders, pp 255–268, 1992

Henderson D, Campo P, Subramaniam M, Fiorino F: Development of Resistance to Noise. Noise Induced Hearing Loss (eds. Dancer A, Henderson D, Salvi RJ, Hamernik R), Mosby Year Book, pp 476–488, 1992

Salvi RJ, Henderson D, Boettcher FA, Powers NL: Functional Changes in Central Auditory Pathways Resulting From Cochlear Diseases. Mosby Year Book, pp 47–60, 1992

Subramaniam M, Henderson D, Campo P, Spongr V: The Effect of "Conditioning" on Hearing Loss From A High Frequency Traumatic Exposure. Hearing Research 58:57–62, 1992

Danielson R, Henderson D, Gratton MA, Bianchi L, Salvi RJ: The Importance of "Temporal Pattern" in Traumatic Impulse Noise Exposures. J Acoust Soc Am 90:209–218, 1991

Campo P, Subramaniam M, Henderson D: The Effect of "Conditionaling" Exposures on Hearing Loss from Traumatic Exposure. Hearing Research 55:195–200, 1991

Subramaniam M, Campo P, Henderson D: The Effect of Exposure Level on the Development of Progressive Resistance to Noise. Hearing Research 52:181–188, 1991

Subramaniam M, Campo P, Henderson D: Development of Resistance to Hearing Loss from High Frequency Noise. Hearing Research 56:65–68, 1991

Henderson D, Subramaniam M, Gratton MA, Saunders SS: Impact Noise: The Importance of Level, Duration, and Repetition Rate. J Acoust Soc Am 1350–1357, 1991

Henderson D, Farzi F, Danielson R: The Concept of Critical Level and Impulse Noise. Environmental International Vol 16 353–361, 1990

Fiorino F, Gratton MA, Subbanna M, Bianchi L, Henderson D: Physiological Mechanism Underlying the Progressive Resistance to Noise Induced Hearing Loss. 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

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 239–254, 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

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, 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, Hamernik RP, Ahroon WA: Neural Correlates of Sensorineural Hearing Loss. Ear and Hearing 4:115–129, 1983

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

Hamernik RP, Henderson D, Salvi RJ: New Perspectives on Noise-Induced Hearing Loss. Raven, Press, New York, NY, 1982

Functional Correlates of Cochlear Injury

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Program Area: *Noise-Induced Hearing Loss*
Grant Number: *5 R01 OH02128-08*
Start & End Dates: *09/01/84 – 05/31/94*
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Importance to Occupational Safety and Health

The laboratory studies of noise-induced hearing loss in animal subjects and the relation with cochlear pathology directly address the long-term research goals described by 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 address the interaction between aging and noise induced hearing loss.

Measures of hearing sensitivity obtained by positive-reinforcement operant conditioning techniques provide accurate assessment of hearing sensitivity in appropriately trained subjects. Combined with morphometric evaluation of cochlear damage produced by noise exposure, these laboratory studies provide important information about the precise relation between specific noise exposure parameters, i.e., level, duration, schedules, pattern, and the resultant histopathology that is not attainable in human subjects.

Acoustic measures made from ear canals of unanesthetized chinchillas (acoustic inter modulation distortion products and otacoustic emissions) before and after noise exposure will help elucidate cochlear mechanisms and may lead to an objective test for cochlear function.

Field studies of noise exposure and hearing levels of workers exposed at levels below a time-weighted average of 85 dBA provide important baseline data for comparison of groups of exposed individuals to determine the relative contribution of occupational noise exposure to the hearing levels of the groups.

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 otacoustic emissions and acoustic distortion products are being made from the ear canals of all subjects. Finally, an attempt is being made to develop a national "Annex B" comparison database for U.S. industry, for use with the new International Standard R 1999.

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 examination of the cochlea. Behavioral measures of thresholds and discrimination ability are controlled by newly-developed virtual instrumentation software which is programmed on a Macintosh II computer system. Acoustic measures are made with small probe microphones and receivers positioned in the ear canal of the unanesthetized animal. Audio metric data from industry are accumulated in a large database on a Macintosh computer, and statistical software packages are used for data selection and analysis.

Significant Findings

Some of the significant findings of the project include:

1. Asymptotic threshold shifts appear to set an upper bound on permanent threshold shifts. Animals exposed continuously for the equivalent of a working lifetime of noise (9 years continuously) do not suffer additional hearing losses as the exposure continues; even after very long exposures some recovery is always observed after cessation of the noise, indicating a persisting temporary component to the hearing loss. Animals exposed for long periods, allowed to

recover, and then re–exposed lose hearing much more slowly than they did on the initial exposure, indicating that the surviving sensory cells are "toughened" by long–term exposure to noise and become much more resistant to subsequent exposures.

2. Interrupting an exposure with rest is protective. Exposures with quiet periods interspersed produce less hearing loss and less cochlear damage 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 interrupted exposure, hearing sensitivity recovers even though the exposure continues. That is, some of the sensory elements of the inner ear can "toughen" themselves against further insult by noise. Physiological evaluation of auditory nerve fiber thresholds confirmed that recovery of up to 30 dB of sensitivity can occur, and the locus of the phenomenon is peripheral, probably at the level of the hair cell.
4. The mechanism of the recovery phenomenon differs, depending upon the primary site of stimulation of the cochlea. Low–frequency exposures (octave band of noise centered at 0.5 kHz, 95 dB SPL, 15 minutes per hour) result in considerably more recovery than high frequency exposures (octave band of noise centered at 4.0 kHz, 86 dB SPL, 15 minutes per hour). These findings suggest different mechanisms of recovery with different time constants.
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 quiet environments 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.
7. Distortion product otacoustic emissions (DPOAE) measured during and after interrupted noise exposure behave differently than behaviorally–measured threshold shifts. DPOAE continue to deteriorate during interrupted noise exposure even when thresholds are recovering; after noise exposure DPOAES continue to recover for as long as 90 days after noise exposure, even though threshold recovery is complete by 10 days. Finally, correlation between DPOAE shifts and outer hair cell loss is poor, implying that the DPOAE may not be a sensitive indicator of hearing function or outer hair cell integrity.

Publications

Bohl CD, Clark WW: The Effect of Hand Held Radio Operation on Audio Dosimeters. Am Ind Hyg Assoc J 54:127–134, 1993

Clark WW: Hearing: Effects of Noise. Otolaryngology Head and Neck Surgery 106:669–676, 1992

Clark WW, Bohl CD: Corrected Values for Annex B of ISO 1999. J Acoust Soc Am 91:3064–3065, 1992

Clark WW: Noise Exposure and Hearing Loss in Children and Youths. ASHA 34:93, 1992 (Abstract)

Cherow E, Clark WW, Berger E: A National Noise Abatement Strategy for the United States. ASHA 34:187, 1992 (Abstract)

Clark WW: The ASA's Role in Preventing Nonoccupational Hearing Loss in the United States. J Acoust Soc Am 92:2357, 1992 (Abstract)

Clark WW: Noise Exposure in Children and Youths. J Acoust Soc Am 91:2375, 1992 (Abstract)

Royster L, Lipscomb D, Clark WW, Dobie R, Jayne T: The Expert Witness in Heating Loss Claims and Other Hearing Related Actions. Proceedings of the 1992 Hearing Conservation Conference, sponsored by the National Institute for Occupational Safety and Health and the National Hearing Conservation Association, Cincinnati, OH, p. 3, 1992 (Abstract)

Clark WW, Bohne BA: Hearing Loss and Cochlear Damage from Interrupted Exposure to Noise. In: Noise–Induced Hearing Loss, (eds. A Dancer, D Henderson, R Salvi, R Hamernik), Mosby, St. Louis, pp. 445–455, 1991

Clark WW: Recent Studies of Temporary Threshold Shift (TTS) and Permanent Threshold Shift (PTS) in Animals. J Acoust Soc Am 90:155–163, 1991

Clark WW: Noise Exposure and Hearing Loss from Leisure–time Activities: A Review. J Acoust Soc Am 90:175–181, 1991

Clark WW: A Head Start on Hearing Loss. Spectrum: The National Hearing Conservation Association Newsletter 8:1–6, 1991

Clark WW: Effect of Amplified Music on Hearing of Children. In: Hearing Before the U.S. House Select Committee on Children, Youth, and Families., "Turn it Down: Effects of Noise on Hearing Loss in Children and Youth. July 22, 1991. US Government Printing Office, Washington pp. 54–67, 1991

Clark WW, Lambert PR: Hearing Loss: Occupational and Nonoccupational. In: Combatting Noise in the 90's: A National Strategy for the United States. American Speech–Language Hearing Association, Washington, pp 29–31, 1991

Clark WW: Amplified Music from Stereo Headsets and Its Effect on Hearing. Hearing Instruments 41(10):29–30, 1990

Bohne BA, Clark WW: Studies of Noise–Induced Hearing Loss Using an Animal Model. Hearing Instruments 41(10):13–16, 1990

Clark WW, Popelka GR: Response to Dr. Kryter's Letter Concerning the Article, "Hearing levels of Railroad Trainmen". Laryngoscope 100:1136–1138, 1990

Clark WW: Role of Non–occupational Exposure in Diagnosing Occupational NIHL. Proceedings of the 1992 Hearing Conservation Conference, sponsored by the National Institute for Occupational Safety and Health and the National Hearing Conservation Association, Cincinnati, OH, p. 167, 1991 (Abstract).

Clark WW: Noise and Leisure Activities. Proceedings of the NIH National Consensus Conference of Noise. Office of Medical Applications of Research and National Institute on Deafness and Other Communication Disorders, 1990

Clark WW, Popelka GR: Hearing Levels of Railroad Trainmen. Laryngoscope 99:1151–1157, 1989

Clark WW, Bohne BA, Reilly TJ: Effects of Periodic Rest on Hearing Loss and Cochlear Damage Following Interrupted Exposure to High–Frequency Noise. Abstracts of the 12th Midwinter Meeting of the Association for Research in Otolaryngology, pp. 218–219, 1989

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)

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

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

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

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Importance to Occupational Safety and Health

The noise research supported by this continuing grant began in August 1993 after concluding a previous three–year project. Thus the summary descriptions that follow reflect the results of two different but related kinds of noise studies. Industrial noise environments are typically characterized by high levels of impact noise that are superimposed on a continuous noise background producing a complex temporal signal. These high kurtosis noise environments pose an unusually high risk of hearing loss to the repeatedly exposed individual. Current noise measurement practice relies upon a time averaged energy metric (e.g., L_{eq}) which has been shown to be inadequate to characterize a long–term noise exposure. Alternatives to such metrics that are highly correlated with the magnitude and frequency specificity of hearing loss are desirable for industrial hearing conservation practice. Furthermore, hearing loss in industrial workers accumulates from repeated daily (interrupted) exposures to excessive noise over a long period of employment. Most strategies designed to estimate hearing loss rely either upon extrapolations from experimental data acquired from short–term acute exposures or from noninterrupted long–term noise exposures or from epidemiological data with its typically 70 dB or more across–subject variability. Recent discoveries show that the peripheral auditory system can modulate the effects of noise exposure as much as 40 dB. These effects are believed to be partially medicated by the outer hair cell motor system which can be activated by a low–level noise exposure that precedes a hazardous noise exposure, or by interrupting a daily noise exposure regime. The outer hair cell bi–directional transduction system is also responsible for generating cochlear emissions which are now being intensively studied because of their potential use as a noninvasive and objective diagnostic test for noise–induced changes in outer hair cell function. Although exposure to high–level impact noise continues to pose a problem to hearing in many industrial environments, there is virtually no experimental data on the accumulation of hearing loss from interrupted high–level impact noise and relatively little data available on the relation between cochlear emissions and noise–induced sensory cell pathology. Similarly, our knowledge of how low–level noise outside the work place affects hearing loss acquired in the work environment is inadequate.

Objectives

Our noise research program is designed to study the types of issues that are summarized above in an animal (chinchilla) model. The objectives of this research are: (1) to extract metrics from a complex noise environment that correlate with the magnitude and frequency specificity of the hearing loss resulting from prolonged exposure to such noise environments; (2) to characterize the hearing loss and cochlear pathology resulting from interrupted impact and complex noise (i.e., non–Gaussian, high kurtosis noise) in order to determine the extent to which temporal factors of an exposure affect trauma; and (3) to develop correlations among the cubic distortion product emissions (3DPE), permanent threshold shift and sensory cell pathology in an effort to determine the extent to which the 3DPE can be used as a diagnostic or screening tool for persons at risk of acquiring noise–induced hearing loss.

Methodology

The chinchilla is being used as an animal model. Hearing thresholds and 3DPE input/output functions are obtained prior to exposure and at regular intervals following exposure up to 30–days postexposure. After the effects of the acoustic insult have stabilized, surface preparation histology is used to quantify the sensory cell population. The exposure paradigms include interrupted and noninterrupted noise presentations for either 5 or 20 days. Exposures are balanced for total energy so that comparisons based upon energy can be made. The noise stimuli are computer generated and consist of: (a) narrow band (400 Hz) impacts with center frequencies between 0.5 and 8.0 kHz. These frequencies were chosen to characterize the cochlear protective (toughening) mechanisms across a broad extent of the basilar membrane; (b) broad band impacts; and (c) various complex high kurtosis noises all having the same L_{eq} and spectrum but differing in their statistical properties.

Significant Findings

1. A series of five noise exposures each having the same L_{eq} = 100 dB and long–term spectrum, but varying statistical properties i.e., from Gaussian where the time domain kurtosis $\beta(t) = 3$ through various increasing values of $\beta(t)$. The impulsive components of the non–Gaussian noises had various spectral configurations, while the peak pressures and the inter impulse intervals were controlled though probability functions. Despite equivalent energies and spectra in each of the five exposures, the resulting permanent threshold shifts and sensory cell losses varied in magnitude and frequency specificity in a manner that was not predictable on the basis of conventional measurements or $\beta(t)$. However, computation of the frequency domain kurtosis $\beta(f)$ for each of the exposures using various algorithms showed that $\beta(f)$ could be used to predict the relative magnitude and frequency specificity of the hearing loss and outer hair cell loss. Taken together these experiments show that while the temporal structure of a continuous, uninterrupted exposure is an important variable in determining trauma, conventional measures of an exposure such as L_{eq} are not sufficient to predict the nature of trauma. The $\beta(f)$ metric however, shows a high correlation with trauma and may be a useful measure in industrial noise assessment.
2. Exposure of chinchillas to broad band, high–level (107, 113, 119, or 125 dB peak SPL) impact noise (1/s) on an interrupted 6h daily schedule over 20 days has shown that pure tone thresholds measured immediately following each daily exposure improve as much as 30 dB despite the continuing noise exposure. The time constant of this recovery effect (toughening) and the magnitude of the effect are related to test frequency (impact spectrum) and the exposure energy. The trauma, quantified by permanent threshold shifts and sensory cell losses, produced by the interrupted exposure paradigm is generally less than that produced by an equal–energy uninterrupted exposure. The wide variations in the temporal pattern of threshold shift across similarly exposed animals suggest that the toughening effect reflects the underlying susceptibility of that animal to noise trauma.

Publications

Ahroon WA, Davis RI, Hamernik RP: The Role of Tuning Curve Variables and Threshold Measures in the Estimation of Sensory Cell Loss. Audiology 32:244–259, 1993

Davis RI, Hamernik RP, Ahroon WA: Frequency Selectivity in Noise–Damaged Cochleas. Audiology 32:110–131, 1993

Ahroon WA, Hamernik RP, Davis RI: Complex Noise Exposures: An Energy Analysis. J Acoust Soc Am 93:997–1006, 1993

Hamernik RP, Ahroon WA, Hsueh KD, Lei SF, Davis RI: Audiometric and Histological Differences between the Effects of Continuous and Impulsive Noise Exposures. J Acoust Soc Am 93:2088–2095, 1993

Hamernik RP, Ahroon WA, Davis RI, Lei SF: Hearing Threshold Shifts from Repeated Six–hour Exposure to Impact Noise. J Acoust Soc Am 94, in press, 1993

Ahroon WA, Lei SF, Davis RI, Hamernik RP: The Use of Frequency Domain Kurtosis in the Assessment of Industrial Environments for Hearing Conversation Purposes. J Acoust Soc Am 91(A):2381, 1992

Hsueh KD, Hamernik RP: Performance Characteristics of a Phase Domain Approach to Random Noise Synthesis. J Noise Control Engineering 36(1):18–32, 1991

Preventing NIHL In Construction Workers

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Importance to Occupational Safety and Health

The purpose of this project is to prevent noise–induced hearing loss (NIHL), an irreversible impairment with significant monetary and personal costs, in construction workers through improved training in use of hearing protection (HP). The training will be based on a conceptual model, the Health Promotion Model (HPM) and specific to construction workers (CWs).

The Department of Public Health has estimated that one quarter of the five million CWs in the U.S. are exposed to average daily noise levels above 85 dBA (USDPH, 1988); yet no data regarding prevalence of NIHL or level of use of HP by CWs has been reported. While it is preferable to reduce this noise exposure through engineering controls, it is not feasible to eliminate all harmful noise. However, consistent use of HP equipment prevents NIHL. CWs represent a diverse and mobile population, exposed to various types of noise in conjunction with other safety hazards, on multiple and variable job sites. Therefore, knowledge of the predictors of these workers' use of HP is essential to the design of more effective training programs.

This study will provide needed data covering five different areas: (1) the degree of hazardous noise exposure as perceived by CWs; (2) the frequency of use of HP by CWs; (3) the strongest predictors of use of HP by CWs; (4) recruitment of CWs into research studies through their training programs; and (5) worker behavior related to personal involvement in safety precautions within a comprehensive health promotion framework.

Additionally, the proposed study will result in a customized training program for the prevention of NIHL in CWs through the increased use of personal HP. By developing the individual worker's consistent use of protective equipment, safety measures can be transported from construction site to construction site, despite the limited options for environmental control.

Objectives

This project has four specific aims: (1) identify the most important predictors of CW's use of hearing protection, specifically for carpenters, operating engineers, and plumbers/pipefitters; (2) use the identified predictors of CW's use of HP to adapt the training program already developed for factory workers to the needs of CWs; (3) assess the effect of the training program on CWs' use of HP; and (4) revise the training program as indicated and make it available for general use in training CWs.

Methodology

This study will be conducted with two distinct samples, a regional sample and a national sample, in three phases: (1) a cross–sectional correlational study will identify predictors of selected CWs' use of HP (carpenters, operating engineers, and plumbers/pipefitters); (2) the training program prepared for factory workers will be revised to incorporate the predictors of CWs' use of HP and pilot–tested with CWs in this region; (3) the effect of the training program on the use of HP will be measured in both the regional and national samples through random assignment of workers to a Solomon Four–Group experimental design.

Significant Findings

None to date.

Stress in One Occupational Group: Teachers

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Funding Level: *$114,399 ($599,479 Cum)*

Importance to Occupational Safety and Health

Little longitudinal research has been devoted to effects adverse working conditions exert on mental health and job–related morale. Teaching is an apt context in which to study these effects because the working conditions teachers encounter vary widely. An innovative feature of this study is that it follows newly appointed teachers through three years of work–force experience. Because the study begins before the women teachers entered the work force and includes a nonteacher comparison group, selection–based effects could be assessed. The study is also important because of the profession's critical role in our nation's social and economic life.

Objectives

1. To compare the mental health (e.g., depressive symptoms) of recent women college graduates who enter the teaching profession with that of similar graduates who enter other occupations.
2. To identify job conditions that affect the mental health, health behaviors (e.g., psychophysiologic symptoms––headaches, etc.), and morale (e.g., job satisfaction) of newly appointed women teachers.
3. To ascertain the effects of different types of resources, including personal dispositions (e.g., locus of control––an individual's belief about the degree to which people control their circumstances), social support, and coping behaviors, on health outcomes in teachers.
4. To study the formation of one social resource, social support from colleagues.

Methodology

The project recruited subjects from two types of senior–year college classes: education classes that students typically attend enroute to teacher certification and psychology classes that are largely taken by students with little intention of entering the teaching profession. Education and psychology students tend to be similar on a number of social demographic characteristics (e.g., predominance of females). The colleges were selected because they have had a record of supplying teachers to New York area school districts. Subjects were part of the classes of 1987, 1988, 1989, and 1990.

Participants completed specially constructed survey instruments in the summer following graduation (Time 0), the fall (Time 1), and the following spring (Time 2). They also completed instruments during a second summer (Time 3), a second fall (Time 4), a second spring (Time 5), a third fall (Time 6), and a third spring (Time 7). With the Time–0 survey, the project collected critical preemployment data on the various outcome measures (e.g., depressive symptoms) including expected job satisfaction. Outcome data and data on working conditions were collected during Times 1 and 2, and Times 4 to 7.

Significant Findings

The findings presented here include women teachers who met two criteria: they taught full–time during two consecutive data collection periods and did not change schools between those two periods. For the purpose of examining women with maximal exposure histories, women who taught part–time and women who changed from one school to another between assessment periods were excluded.

1. In a comparison of the women who went on to obtain positions in the "best" schools, the "worst" schools, and schools of intermediate levels of adversity, there were no differences in preemployment levels of depressive symptoms. These women also did not differ from control women who obtained full–time nonteaching jobs. This finding is important because it indicates that self–selection or selection by administrative gatekeepers did not account for later differences.
2. Once the women obtained full–time jobs, those who went on to obtain jobs with the most adverse working conditions (e.g., student violence, administrator insensitivity) had the highest levels of depressive symptoms in the fall and spring. The women who obtained jobs in the best run schools had the lowest levels of depressive symptoms. The women who obtained jobs in the schools of intermediate adversity and the women who obtained nonteaching jobs showed intermediate symptom levels.

We conducted lagged regression analyses in which we predicted future problems (e.g., fall of the teacher's third year) from working conditions measured during the prior data collection period (e.g., the spring to the teacher's second year). Preemployment factors, social demographic characteristics, and nonwork stressors were controlled statistically. The results indicated that adverse school conditions were generally related to future depressive symptoms, satisfaction with work, motivation to remain in teaching, and psychophysiologic symptoms.

3. These analyses also tended to show that social support from nonwork sources was related to fewer depressive and psychophysiologic symptoms and better self–esteem during the first year. After year one, however, nonwork social support was related only to better self–esteem. Over time, job satisfaction was the main outcome to which social support from colleagues was related. The most important factor predicting colleague support was social support from outside sources. The personality factor locus of control was not related to the outcomes.
4. Individual coping behaviors tended not to be related to reduced problems. The effects of coping behaviors were swamped by the quality of working conditions.

Conclusions. The factors that adversely affect teachers' well–being are preventable. They include student violence and disrespect as well as disrespectful behavior on the part of administrators. The findings underline the relative importance of efforts aimed at "environmental protection" in comparison to more purely "personal solutions." The findings indicate that private solutions in the teacher's coping repertoire (e.g., use of discipline, advice seeking, etc.) are at best of limited efficacy. What was clear, however, was that the teachers fortunate enough to obtain jobs in safe, well–run schools had fewer depressive symptoms than their colleagues in worse–run schools. Moreover, the symptom picture of teachers who obtained jobs in the better–run schools compared favorably to those same women's preemployment symptom picture. In order to ensure the supply of well–functioning teaching professionals, it is important to make every school safe and well run.

Publications

Schonfeld IS, Rhee J, Xia F: Some Methodologic Issues in Occupational Stress Research: Examples From Research in One Occupational Group. In: Job Stress 2000: Emerging Issues, (eds. GP Keita, S Sauter), Washington, DC, American Psychological Association, in press, 1994

Schonfeld IS: Burnout in Teachers: Is It Burnout or Is It Depression? Human Stress: Current and Selected Research, in press, 1994

Schonfeld IS: Assessing Stress in Teachers: Depressive Symptoms Scales and Neutral Self–reports on the Work Environment. In: Work and Well–being: Assessments and Instruments for Occupational Mental Health, (eds. J Quick, L Murphy, J Hurrell, Jr.), Washington, DC: American Psychological Association, pp 270–285, 1992

Schonfeld IS: A Longitudinal Study of Occupational Stressors and Depressive Symptoms in First–year Teachers. Teaching and Teacher Education 8:151–158, 1992

Schonfeld IS: Dimensions of Functional Social Support and Psychological Symptoms. Psychological Medicine 21:1051–1060, 1991

Schonfeld IS, Ruan D: Occupational Stress and Pre–employment Measures: The Case of Teachers. Journal of Social Behavior and Personality 6:95–114, 1991

Schonfeld IS: Coping with Job–Related Stress: The Case of Teachers. Journal of Occupational Psychology 63:141–149, 1990

Schonfeld IS: Distress in a Sample of Teachers. Journal of Psychology 123:321–338, 1990

Schonfeld IS, Shaffer D, Barmack JE: Neurological Soft Signs and School Achievement: The Mediating Effects of Sustained Attention. Journal of Abnormal Child Psychology 17:575–596, 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

Relative Health Risks of Diesel Emission Control Systems

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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 with and without diesel emissions control devices 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

Objectives

The overall objectives of this project were: (1) to obtain estimates of diesel pollutant levels in underground coal mines when DPM emission control devices are not in use, to include polynuclear aromatic hydrocarbons (PAH) and biological activity; (2) to assess the effects of using DPM emission control systems on these pollutants in laboratory tests; and (3) to obtain estimates of the effectiveness of using various DPM emission control devices on these same pollutants in a metal mine and in a coal mine.

Methodology

Samples from four dieselized underground coal mines without DPM control devices were collected by BOM personnel using Hi–volume samplers equipped with inertial impactors to collect size–differentiated particle samples. Particles ≤ 1 um in size were considered to be primarily of diesel origin. Samplers were located at the section intake and in the haulageway near where diesel shuttle cars turned around to dump their loads. 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.

Samples were also collected and analyzed using similar techniques from (1) a dieselized metal mine where a catalyzed diesel particle filter (CDPF) and an oxidation catalytic converter (OCC) were used together and (2) a dieselized underground coal mine where a disposable diesel exhaust filter (DDEF) was used.

Laboratory samples for DPM and semi–volatile organics were also collected at the BOM in two separate studies: (1) with and without a CDPF; and (2) with and without an OCC. Both filter (DPM) and XAD–2 resin (XAD–2 resin organic component or XOC) samples were collected, with organic material removed from both types of media by Soxhlet extraction with dichloromethane. The CDPF studies were conducted using a low sulfur (0.039 wt. percent) fuel. The OCC studies were conducted with six different fuels varying in sulfur and aromatic levels and cetane number.

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 compounds chosen for quantification due to their known or suspected health effects included fluoranthene, chrysene, benz[*a*]anthracene, benzo[*a*]pyrene, 1–nitropyrene, 2–nitrofluorene, and 3–nitrofluoranthene. Sulfate levels were determined by ion chromatography of aqueous extracts from the filters following their Soxhlet extraction for SOF removal. Unfractionated SOF and XOC and some fractions were tested for biological activity using the microsuspension version of the Ames assay.

Significant Findings

Estimates of Diesel Pollutant Levels in Underground Coal Mines – The DPM, PAH, and mutagenic activity levels represented potential highest in–mine values that would occur when diesel equipment was operating in a given area. The DPM values (mean/mine range of 0.9 – 1.9 mg/m^3) were typically at the upper end of values obtained with other, more personal–type sampling methods. In most cases, the mine atmosphere levels of DPM, SOF, PAH, and mutagenicity were statistically similar for all four underground coal mines, thus providing a range of values that might be expected to occur when

diesel vehicles without DPM emission control devices are operating. Use of the DDEF in another coal mine resulted in at least 50 percent reductions in all diesel emissions' concentrations in the haulageways.

The differences in levels between the mines were likely related to differences in parameters such as vehicle type, mine ventilation efficiencies, fuel composition, and engine design, operation, and maintenance, with engine operation and maintenance probably being the major factor. The lowest levels of SOF and associated PAH were found at the mine with well–maintained engines operating at high loads; the highest levels of these parameters were found at the mine with relatively poorly maintained vehicles spending a considerable amount of time idling.

Laboratory Studies with DPM Emission Control Devices – Laboratory–generated data were found to be reliable for estimating in–mine levels in dieselized underground mines. When making such comparisons, it is particularly important that the laboratory data have been generated from engine operating conditions that closely resemble the diesel engine operation in the comparison mines. The data obtained from a transient cycle designed to simulate haulage vehicle operation closely resembled the coal mine data where such haulage vehicles operate. The data from a steady–state cycle designed to simulate operation of load–haul–dump vehicles, such as would be used in metal mines, did not as closely resemble the actual data from the coal mines.

When used in conjunction with a low sulfur (<0.05 wt percent) fuel, it was estimated that use of the tested CDPF in underground mines could result in at least 90 percent reductions in DPM levels, with comparable effects on other diesel exhaust components. The CDPF was slightly less effective in reducing XOC compared to SOF (99 percent versus 89 percent, respectively), although both reductions were significant. The CDPF removal efficiency for DPM–associated PAH was ≥98 percent for both transient and steady–state operation. Only fluoranthene and pyrene were found with the XOC with or without the CDPF. Over the transient cycle, the CDPF reduced the DPM–associated mutagenicity levels by 75 percent and the vapor phase organics–associated levels by 80 percent. The steady–state weighted cycle produced an average 69 percent reduction in SOF–associated mutagenicity levels. This difference between reductions in organics (up to 99 percent) and mutagenicity levels (up to 80 percent) was related to presence of active compounds such as nitro–PAH.

When used in conjunction with a low sulfur fuel, use of the tested OCC in underground mines could also have a significant impact on reducing DPM levels as well as other emission components. Using a transient test cycle simulating potentially worst case operation of the OCC, from 30 to 60 percent reductions were found in all measured emissions. Some differences in emissions due to fuel composition were also noted.

Effects of a CDPF and an OCC in an Underground Metal Mine – Use of a combined CDPF/OCC in an underground metal mine resulted an approximately 50% reductions in DPM, SOF, and PAH concentrations. These less–than–expected reductions (based on data from the laboratory studies) may have been due to the fact that the area being sampled was heavily impacted by air from areas in the mine where dieselized vehicles without this combined control devices were in use. Mutagenic activity concentrations (revertants/m^3) increased by about 250% with CDPF/OCC use, reflecting over 500% increases in activity on a mass basis (revertants/ug SOF). This increase appeared to be due to increases in nitro–PAH with use of the CDPF component of the control device.

Publications

Cantrell BK, Rubow KL, Watts WF Jr, Bagley ST, Carlson DJ: Pollutant Levels in Underground Coal Mines Using Diesel Equipment. Proc of the 6th US Mine Ventilation Symposium, Society for Mining, Metallurgy, and Exploration, Inc, Salt Lake City, Utah, in press, June 21–23, 1993

Bagley ST, Baumgard KJ, Gratz LD: Polynuclear Aromatic Hydrocarbons and Biological Activity Associated with Diesel Particulate Matter Collected in Underground Coal Mines. Proc of Bureau of Mines Information and Technology Transfer Seminar on Diesels in Underground Mines: Measurement and Control of Particulate Emissions, Bloomington, Minnesota, pp. 40–48, September 29–30, 1992

McClure BT, Bagley ST, Gratz LD: The Influence of an Oxidation Catalytic Converter and Fuel Composition on the Chemical and Biological Characteristics of Diesel Exhaust Emissions. SAE Technical Paper Series No 920854, 1992

Bagley ST, Baumgard KJ, Gratz LD, Bickel KL, Watts WF Jr: Effects of a Catalyzed Diesel Particle Filter on the Chemical Biological Character of Emissions from a Diesel Engine Used in Underground Mines. SAE Transactions 100:1578–1589, (SAE Technical Paper Series No 911840), 1991

Bagley ST, Baumgard KJ, Gratz LD: Comparison of IN–mine and Laboratory–generated Diesel Particulate Matter, Biological Activity, and Polynuclear Aromatic Hydrocarbon Levels. Proc of 3rd Symposium on Respirable Dust in the Mineral Industries, Pittsburgh, Pennsylvania, 61–70, October 17–19, 1990

Computer Simulation of Push-Pull Systems

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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 eg, 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

An upwind finite element algorithm employing a penalty approximation has been used to approximate the three–dimensional velocity field. Experimental validations of the predictions are made with hot–film anemometry, smoke wire flow visualization techniques, and hood capture efficiency using sulfur hexafluoride as the tracer and infrared spectrophotometry as the detection method.

Significant Findings

Computer velocity predictions are in good agreement with values measured using hot–film anemometry. Flow visualization of this simple push–pull flow has been achieved by using a smoke wire in the plane of the cross draft. The resulting estimate of the jet trajectory is in excellent agreement with computer simulations. Turbulence kinetic energy is not well predicted by the code particularly in the vicinity of the hood reflecting either an inadequate turbulence model or insufficient gris resolution.

Application of Neural Networks for Process Fault Diagnosis & Safety

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Importance to Occupational Safety and Health

The study of fault detection and diagnosis is concerned with designing systems that can assist human operators in detecting and diagnosing process failures in order to prevent accidents. As modern chemical plants are extremely complex they are more vulnerable to failures, as witnessed by the recent chemical plant related accidents. 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, occurring on a day to day basis, resulting in many occupational injuries, illnesses, and costing the society billions of dollars every year. During 1983 the Bureau of Labor Statistics has 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 intelligent computer systems that can effectively monitor, diagnose, and control chemical plants. In this project, we propose a neural network–based methodology that has considerable potential in the development of such intelligent systems.

Objectives

The major goal of this proposal is to research and demonstrate a novel approach based on Neural Networks for the design of chemical process hazard detection, prevention, and control systems. Fault detection and diagnosis using neural networks is achieved by exploiting their non–linear pattern classification properties. This diagnostic ability crucially depends upon the discrimination of decision regions corresponding to various fault classes. The delineation of decision regions for a given number of fault classes, in turn, hinges on several factors, such as the number of input and hidden nodes, the type of activation function employed, noise in sensor measurements, the extent and nature of training, etc. Further, it is also important to examine the ability of neural nets in detecting and diagnosing faults during process transients by extracting key qualitative features of the underlying process trend. In this project, we propose to examine these central issues.

Methodology

We have built a dynamic simulator of a chemical reactor–distillation column system which is used to simulate a wide variety of faults and dynamic process trends. Using this as a test bed, we have been investigating a variety of neural network architectures to analyze their classification characteristics, their ability to deal with dynamic and noisy sensor data, and so on.

Significant Findings

In the first year of the project, we developed a hierarchical representation framework that can model process trends at different levels of detail to address the problem of extracting key qualitative features from noisy data to aid in fault diagnosis. We also demonstrated the superiority of ellipsoidal neural nets for representing bounded fault classes.

In the second year of the project, the following important contributions have been made following up on our hierarchical framework:

- Fault diagnosis during dynamic process transients using the hierarchical trend analysis framework through the use of moving window schemes.

We have demonstrated that a properly trained network can detect abnormal process conditions soon after they appear, thus facilitating early diagnosis and supervisory control actions.

- Evaluation of the neural network approach in the presence of noisy and uncertain sensory data.

This is a very important issue from the industrial perspective. Much progress was made here with the aid of a distillation column–reactor case study. We have shown that neural nets are quite noise–tolerant and can diagnose successfully in the presence of considerable random noise. We are currently exploring the performance of the neural nets for a more complex industrial case study under a variety of dynamic transients in the presence of process uncertainties and noise to quantify their performance.

- Explore further the use of ellipsoidal nets and investigate issues concerning the design of the ellipsoids, network decomposition strategies etc.

We have developed a network and problem decomposition scheme to reduce the complexity in large–scale fault diagnosis problems. The technique involves input space reduction through the use of principal component analysis and hidden nodes specialization. The results have been very encouraging so far. We are currently focusing on the issue of ellipsoids design to incorporate a priori probabilities and predefined error bounds.

Publications

Kavuri S, Venkatasubramanian V: Neural Network Decomposition Strategies for Large Scale Fault Diagnosis. (Eds. Morari and Morris), Special Issue of Intl J Control, in press, 1994

Kavuri S, Venkatasubramanian V: Using Fuzzy Clustering and Ellipsoidal Units in Neural Networks to Improve Fault Classification. Computers and Chemical Engineering 17(8):765–784, 1993

Emission Factor Development for Intermittent Workplace Sources

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Importance to Occupational Safety and Health

The conceptual thrust of this proposal is to develop a method for generalizing the design of engineering control of workplace hazards. In particular, we are developing emission factors, based on field observations, for four types of commonly encountered, hazardous, open–tank processes: vapor degreasing, electroplating (chromium and copper plating), offset printing, and wave soldering.

Objectives

The value of the emission factor approach is that the effect of the particular interior space in which the data are collected is removed. The factors are developed from the area concentration pattern surrounding each device while production is taking place, using mathematical models describing a mass balance for the contaminant in order to transform this pattern for a particular source to an emission rate. To systematically describe the variability of emissions, the release rate is related to measures of source activity, process conditions, and equipment geometry. A total of 11 source tests have been carried out consisting of 12 1–hour sampling periods which also include measurements of general and local exhaust ventilation. The results of this study will provide: (1) A compilation of activity–based emission factors for Cr and Cu electroplating, vapor degreasing, wave soldering, and offset printing; (2) A measure of the variability in emissions which can be expected from such processes; (3) Actual determinations, based on an emission mass balance, of control device performance for each of the processes studied; (4) A generalized basis for estimating workplace concentrations from these types of sources; and (5) A mass–balance basis for evaluating control design alternatives.

Methodology

Field tests under production conditions have been carried out on: (1) Three methyl chloroform degreasers in a microcircuit production facility; (2) Four Pb wave soldering lines of different designs in two plants making electronic circuit boards; (3) Cu emissions from an electrolytic copper plating line; (4) Two decorative chrome–nickel electroplating lines; (5) A methylene chloride degreaser; (6) A terpene degreaser using limonene; and (7) Three different offset printing plants using, respectively, sheetfed offset, offset web, and heatset web offset printing processes.

Significant Findings

Average total emissions from three uncontrolled methylchloroform degreasing were determined to be between 0.39 kg/hr and 0.74 kg/hr depending on the model used. The approximate usage inventory value for the same time period was 0.62 kg/hr. Emissions were related to uncovered tank conditions, dragout, and type of parts, and 80% were identified as coming from a single line. Total uncontrolled emissions from three Pb wave soldering lines averaged 50.4 mg Pb/hr. Total lead bath scrapings and dedrossings appeared to be the most important source activity variable with an emission factor of 11 mg/solder cleaning. Average copper emissions and emission factor from electroplating were 29 mg/hr and 0.25 mg/amp•hr; and for sulfur were 59 mg/hr and 0.54 mg/amp•hr. Total emissions from a terpene degreaser were 0.68 kg limonene/hr with an emission factor of 2.2 g limonene/circuit board cleaned. Average uncontrolled emissions from a sheet–fed offset print shop were 0.4 kg VOC/hr; with an emission factor of 30–38 g VOC/press cleaning. Additional printing and wave soldering emission factors are still being developed as well as those for methylene chloride, and chrome electroplating.

Computational Methods in Industrial Ventilation

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Start & End Dates: *07/01/91 – 06/30/94*
Funding Level: *$59,540 ($183,386 Cum)*

Importance to Occupational Safety and Health

This project is designed to bring the methods of computational fluid mechanics to bear on the problem of estimating worker exposure. At the present time the inability to estimate exposure remains a serious deficiency in the design process for contaminant control ventilation systems.

Objectives

The specific objectives are: (1) expand an existing computer code based on discrete vortex methods to predict airflow patterns around a worker and a nearby obstacle; (2) develop predictions of exposure using particle tracking methods; and (3) conduct wind tunnel simulations to validate computer predicted flow patterns and exposure estimates.

Methodology

Significant improvements in parallel and serial algorithms for discrete vortex methods continue to appear in the fluid mechanics literature. These improvements are being integrated into an existing algorithm to improve speed and flexibility. Sulfur hexafluride tracer gas studies using infrared spectrophotometry are used to validate exposure estimates. Smoke wire techniques are used to explore flow patterns around mannequins and objects in the wind tunnel.

Significant Findings

A discrete vortex code (DVM) has been developed employing a boundary integral potential flow solver, for prediction of the time dependent flow around a worker and object. Testing continues to evaluate the stability and convergence of the algorithm. In addition a particle tracking algorithm for estimating concentration fields has been incorporated into the code. Several wind tunnel studies to collect data for model validation are complete. Predictions of concentration are in reasonable agreement with measured values, but further work is needed to specify small-scale turbulent time and length scales. Experimental studies confirm predicted air flow patterns around a worker and obstacle and the algorithm correctly identifies worker orientations leading to reduced exposure.

Permeation Mechanisms of Pesticides Through Materials

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Importance to Occupational Safety and Health

While permeation characteristics of single specific solvent chemicals through gloves and garments are well documented, those for specific pesticides and for pesticides in their emulsion concentrate forms (regarded as the most hazardous forms to handle), have not been intensively investigated. Emulsion concentrates consist of the active ingredient, organic solvents, surfactants, and other adjuvants, and thus constitute a multi component chemical exposure on inhalation, dermal or ingestion exposure. This is important during spraying, on worker field reentry, and when formulating. When several pesticides are coformulated in blends under small shop conditions, permeation characteristics through gloves and garments may be influenced by the prior and concurrent handling of the other formulary components.

Objectives

The hypothesis is: the most permeating constituent of the challenge medium containing a

pesticidal emulsion concentrate regulates the permeation of the pesticide through glove and garment materials.

The studies will allow selection of the appropriate permeation method, the most protective gloves and garments for these formulations, and development of a predictive model.

Methodology

The initial studies will involve the identification and quantification of the inert components and surfactants/adjuvants in the selected emulsion concentrates. The latter are: cap tan, chlorpyrifos, 2,4–D (three forms), endosulfan, malathion, methomyl, methyl parathion, and trifluralin. The selected glove materials are: Butyl, Nitrile, Silver Shield, and Viton. The garment materials are: Barricade, two–ply Saranex–Laminated Tyvek 23–P, Chemrel Max, and Teflon/Nomex/Teflon.

Eight–hour screening studies with two ASTM–type permeation techniques will be performed. One technique involves a I–PTC ASTM–type permeation cell and liquid collection system. The other method utilizes a solid silicone sheet collection method. Challenges will be to the neat chemical if liquid, the neat chemical in the major solvent of the formulation in the presence/absence of surfactant/adjuvant, the emulsion concentrate, and to the aqueous emulsion diluted to its highest spraying concentration. Kinetics studies over two–hour periods at three different temperatures will then lead to measurement of breakthrough times, and steady state rates. Shelf–life studies for materials aged 0.5 and 1.0 years after acquisition will also be performed. A predictive permeation model will be developed.

Significant Findings

Work has been initiated with two malathion emulsion concentrates. The liquid malathion neat chemical behaves like a nonpolar ester and thus permeates Nitrile (lag time 50–85 minutes; 0.41–.37 mg/cm^2/min) and penetrates Latex (causes holes within minutes). The permeation is enhanced by the presence of xylene inert component. Challenge of malathion as aqueous emulsion formulations has necessitated optimization of mixing conditions and selection of an inert collection solvent that also permits solubilization of the malathion. Permeation was still observed at much lower steady state rates and about the same breakthrough times relative to challenges with formulations alone.

Initial studies with formulations containing endosulfan, chlorpyrifos, and methomyl have shown that Nitrile is protective for at least two hours. Lannate had the highest steady state rate. Whereas the formulations having endosulfan and chlorpyrifos contained mesitylene inert components, those for lannate were methanol and propanols. The latter were responsible for the faster breakthrough times and higher steady state rates for methomyl.

Encapsulating Protective Clothing: Work Tolerance

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Program Area: *Control Techniques*
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Start & End Dates: *09/15/93 – 09/14/95*
Funding Level: *$153,499 ($153,499 Cum)*

Importance to Occupational Safety and Health

This is the initiation period of a two–year study of the efficacy, stability and generalizability of a prediction model for work tolerance of workers wearing encapsulating protective clothing (PC) in moderate to warm environments. The project will test and refine a recently developed prediction model and determine the generalizability of this approach to prediction in simulated industrial situations.

Successful completion of this project will contribute to managing personnel engaged in labor requiring encapsulating protective clothing in moderate to warm temperatures. Worker safety will be enhanced, and more efficient worker scheduling can be utilized. Workers currently are required to self monitor, which increases risk and impedes effective work management. Current American Conference of Government Industrial Hygienists TLVs provide little help in this situation (1988–89 ACGIH, 1990). Additionally this proposed project addresses, in part, 5 of the 12 research needs listed in NIOSH Criteria for a Recommended Standard for Occupational Exposure to Hot Environments, Revised Criteria, 1986. Current guidance for worker safety in PC is limited. The results of this study could be immediately useful in maximizing work productivity while minimizing safety risks.

Objectives

The purposes of the proposed study are to (1) test the generalizability, stability, and validity of, and refine the multiple regression equations developed in

the previous study, (Bishop et al, 1994) and (2) Derive new equations as needed for other environments and work conditions.

Both purposes of this study lead to development of a technique for predicting physical work capacity of workers in these situations based upon field measurements gathered in a short-term work task performed in protective clothing in a mild ambient environment. This work will build upon recent work done in our laboratory (Bishop et al., 1994). This prior study extended earlier work of Kenny et al. (1986), and Shvartz et al. (1977) and showed that the work tolerance of 15 subjects wearing protective clothing could be predicted from simple performance measures obtained during bench stepping in a 21°C environment.

Methodology

After medical screening, 50 subjects will be measured during a bench step test of less than 20 minutes duration at room temperature (WBGT = 18°C). Simple data (i.e duration, comfort rating, etc.) from this bench step test will then be used to predict performance on a generic work protocol consisting of 15 min. of treadmill walking at 3 mph followed by 5 min. of arm curls with 14.6 kg of weight referred to as "work" hereafter), with this work sequence repeated on separate days in counterbalanced order under these four conditions:

Environment (WBGT °C)	Workload (L/min)
18	VO2=1.0, continuous
18 work, 18 rest	VO2=1.8 for 30 min, rest 30 min (1.8 +.0.2 @ rest yields 1.0)
26 work	VO2=1.0 continuous
26 work, 26 rest	VO2=1.8 for 30 min, rest 30 min (1.8 +.0.2 @ rest)

Models will be derived and tested for generalizability and stability by comparisons of models across subgroups and treatments.

Significant Findings

None to date.

Communication with Flat-Attenuation Hearing Protectors

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Program Area: *Control Techniques*
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Funding Level: *$114,330 ($114,330 Cum)*

Importance to Occupational Safety and Health

The results of this study are expected to determine noise spectra and ranges of noise levels which are appropriate environments for wearing flat-attenuation hearing protection devices (HPDs). Collected data will also be used to assess efficacy of various speech communication measures for assessment of HPDs.

Objectives

The proposed study is designed to evaluate the relationship between noise attenuation and speech communication effectiveness resulting from wearing flat-attenuation HPDs in several simulated work environments. Various objective and subjective measures will be compared to assess the amount of noise attenuation by the protectors as well as the effectiveness of speech communication between workers wearing the protectors.

Methodology

Sixty subjects will participate in the study. The following measures will be directly obtained or calculated in the study: (1) real-ear attenuation at threshold, (2) sound pressure level reduction, (3) word recognition score, (4) speech intelligibility rating, (5) double-task performance effectiveness, (6) speech level adjustment, and (7) vocal effort.

Significant Findings

None to date.

Predictive Models of Solvent Permeation Through CPC

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Importance to Occupational Safety and Health

Dermatological disease arising from contact with chemicals historically has accounted for a disproportionately large percentage of all cases of chronic occupational illness. Dermal absorption of systemic toxicants is also known to be important for several classes of chemicals and is likely underreported. The use of chemical protective clothing (CPC) is often the only feasible means of protecting workers from dermal contact with toxic chemicals. Yet, our current understanding of the factors affecting the permeation resistance of CPC materials to solvents is very rudimentary. As a result, the protection afforded by a given type of CPC in workplace applications, particularly those involving organic solvents, is rarely known with certainty. The research proposed here entails a comprehensive investigation of solvent permeation through CPC and the development and validation of semi–empirical predictive permeation models for solvents and solvent mixtures.

Objectives

The broad goals of this project are to gain improved understanding of the physicochemical factors affecting the permeation of organic solvents through CPC and to develop broadly applicable and easily implemented models for industrial hygienists to use in selecting CPC when experimental data are not available. More specifically, the project focuses on the development and validation of new models for predicting the equilibrium solubilities and the diffusion coefficients in common CPC materials of a wide range of individual organic solvents and solvent mixtures as a function of the type of solvent and CPC material; temperature; CPC production variables such as the degree of polymer crosslinking; and the nature and concentration of co–solvents. This information will then permit accurate prediction of breakthrough times and steady–state permeation rates as a function of these variables.

Methodology

Permeation and immersion tests are being performed on four types of commercial polymeric CPC materials (i.e., butyl, natural, nitrile and neoprene rubbers) challenged with several organic solvents from each of 14 chemical classes. Binary mixtures are being examined for a representative subset of these solvents. These experimental data will serve as the basis for the models of equilibrium solubilities, diffusion coefficients and permeation rates. Solubility models based on (1) three–dimensional solubility parameters, (2) solvatochromic indices in conjunction with linear solvation free–energy relationships, and (3) molecular group contribution methods are being investigated. Models for diffusion coefficients rely on empirical correlations of measured values with the physical properties and CPC–interaction strengths of the solvents. Modeled solubility and diffusion coefficient values will be used in Fickian models to obtain estimates of solvent breakthrough times and steady–state permeation rates.

Significant Findings

Over 1,300 immersion tests have been performed to date, representing duplicate or triplicate tests of solubility of each of 53 solvents in each of the four types of glove samples at each of three temperatures (25, 35, and 45$_{o}$C). Results show that solubility generally increases with increasing temperature as expected, however, decreases in solubility as well as solubility maxima at the intermediate temperature have also been observed. The development of the solubility models is currently in progress. Immersion testing of selected binary mixtures is also in progress.

Permeation tests are being performed with two automated test systems, each of which can analyze two CPC samples simultaneously. Analyses are performed by gas chromatography using computer–controlled sampling, data acquisition, integration and management functions. A total of 80 permeation tests have been completed. All tests are performed in duplicate and proper calibration and quality control procedures are being followed. Breakthrough times ranging from <5 min to >10 days have been measured. The data set is too small at present for the implementation/validation of the permeation models.

Transport Modeling of Industrial Ventilation

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Program Area: *Control Techniques*
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Funding Level: *$152,013 ($152,013 Cum)*

Importance to Occupational Safety and Health

Accurate, robust computational models must play an integral role in any plan directed towards significantly improving the design and development of ventilation systems. An area in which improved predictive methods are especially critical is contaminant transport in unsteady turbulent flow fields in which the contaminant is comprised of dense particulates. Because dense particles cannot follow the fluctuations of gas–phase turbulence, the range of interactions between the turbulent gas flow and suspended particles are very complex and not particularly well understood at the present time. It is not surprising, therefore, that design of ventilation hoods for applications of particulate removal is for the most part empirical. Consequently, there is no well developed rationale for current design practices and design techniques applicable to large classes of ventilation systems are lacking. Improved predictive capabilities are especially important because the complex interactions between the turbulent gas flow and suspended particles may pose greater risk to industrial workers than is currently accounted for by present day design practices.

Thus, given the complex nature of gas–particle interactions in turbulent flow fields and their impact on industrial ventilation, new predictive methodologies are needed to improve the design and development of these systems. The long–range goal of this research program is therefore development of a new generation of predictive methods for contaminant removal in industrial ventilation applications.

Objectives

The principal objective of the present study is model development for prediction of turbulent flow fields laden with small, dense particles. Specifically, in this work models of particle transport appropriate for large–eddy simulation (LES) of the Navier–Stokes equations is being addressed. A major emphasis of the work is model development in the framework of the most promising approach to turbulence modeling developed within at least the last 10 years: dynamic subgrid–scale modeling.

Because of the complex nature of gas–particle flow fields in industrial ventilation applications, it is unrealistic at this stage to attempt development a general computational methodology suitable for arbitrary ventilation systems. Thus, this effort is directed towards model development in canonical flows containing the essential physics present in actual ventilation systems, viz.\ particle–laden free shear layers.

Methodology

Traditionally, predictive techniques for turbulent gas–particle flows have been limited by deficiencies in not only the particle transport models but also the turbulence models employed in the Navier–Stokes equations. This difficulty has been alleviated in the present work by employing large–eddy simulation of the Navier–Stokes equations as the solution technique for the gas–phase turbulent flow.

Filtering of the Navier–Stokes equations in LES introduces turbulent stresses which cannot be resolved by the computational grid. One of the novel features of this work is parameterization of the subgrid–scale stresses using dynamic subgrid–scale modeling. The novel feature of dynamic modeling is that the subgrid–scale stresses are modeled using information from the resolved scales. This approach has yielded extremely accurate descriptions of several canonical flows. Its application to turbulent two–phase flows represents an important step in furthering the use of LES for engineering applications. The dispersed phase of solid particles is treated in this work using a Lagrangian approach, i.e., the equation of motion is integrated along discrete trajectories for a large ensemble of particles.

Significant Findings

As this work has been recently initiated, the majority of our efforts have been devoted to establishing the foundation for the research. Specifically, we are implementing the numerical methods to be employed in the work and continuing our efforts in further refining dynamic subgrid–scale modeling. Notable in this effort has been application of the dynamic model to rotating turbulent flows; providing yet another example of a class of flows in which the dynamic model correctly accounts for the effect of system rotation on turbulence structure. This is extremely positive from the standpoint of

industrial ventilation applications since the complicated, three–dimensional, time–dependent flow fields are not easily amenable to prediction by traditional methods.

Load Monitoring For Safe Construction

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Program Area: *Control Techniques*
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Funding Level: *$218,678 ($218,678 Cum)*

Importance to Occupational Safety and Health

This project addresses the problem of occupational safety on construction sites. The specific problem addressed in this study is the prevention of the unexpected collapse of partially constructed facilities, in particular multistory reinforced concrete structures which are built using falsework and shoring structures. Over the past 25 years at least 85 such collapses have been documented and reported. The effects of such a collapse can be catastrophic as evidenced by the 1987 collapse of the L'Ambiance Plaza in Bridgeport, CT in which 28 construction workers were killed.

At present there is little detailed guidance in the construction building codes regulating the design and construction of shoring systems for the construction of reinforced concrete buildings. There are also, at present, very few instruments available that can detect, document and provide a warning for dangerous loading conditions on the shoring systems.

The overall results of this project will be the acquisition of load data on shoring systems during construction which can be used in the development of rational design codes. A subsidiary result will be the development and testing of equipment that can possibly be used to provide a real–time early warning and data logging capability for dangerous loading conditions.

Objectives

The overall goals of this project are to develop and implement real–time load and deflection monitoring instrumentation for buildings during construction, to develop an improved understanding of critical construction loading conditions, and to develop guidelines for safe construction practices specifically associated with multistory reinforced concrete construction. The fundamental hypotheses for this work are (1) that the primary cause of construction failures is inadequacy of the temporary support elements such as vertical shores and lateral bracing, (2) that an investigation of load and deflection histories during actual projects can contribute greatly to our understanding of critical loading conditions, and (3) that this improved understanding and invaluable information can be used as the basis for improved construction procedures and guidelines for safe design and construction.

Methodology

The research plan for this project contains two distinct portions. The first involves taking shoring load data at two or three building sites. The load data will be measured with an array of eight or more three–axis load cells. The three axis load cells will enable the measurement of side loads as well as vertical loads. Side loads have been implicated in a number of collapses that involved a loss of lateral stability. The data will be gathered and stored on an optical disk drive for further analysis. The second phase will involve a detailed analysis of the data coupled with computer models of the load distribution in curing concrete structures. The data and structural analysis will then be used with various reliability–based techniques to develop proposed guidelines for shoring design. The proposed guidelines will be presented to the cognizant bodies for comment and possible adoption.

Significant Findings

None to date.

Field Study of Local Exhaust Ventilation Performance

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Program Area: *Control Techniques*
Grant Number: *5 K01 OH00078-03*
Start & End Dates: *09/28/89 – 09/29/93*
Funding Level: *$0 ($138,046 Cum)*

Importance to Occupational Safety and Health

A model which can be used to predict capture efficiency of 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

Measurements were conducted over two days at each of seventeen locations. Local exhaust and general ventilation flow rates, as well as the physical dimensions of the workspace and the degreaser were measured. Solvent concentrations at several locations in the workspace and in the local exhaust duct were measured in one–hour intervals. Crossdraft velocity was measured simultaneously with concentration in two–minute intervals. The concentration results and the ventilation characteristics of the space were used to determine the rate of solvent emission into the workspace using several mass balance models. The local exhaust emission rate was calculated from the duct flow rate and concentration. The ratio of duct emission rate to total emission rate is the hood capture efficiency. The measured crossdrafts, local exhaust hood flow rate, and the area of the tank surface were used in the predictive capture efficiency model for each sampling interval. These were compared with the measured capture efficiencies. Activities involving the degreaser and activities in the vicinity of the degreaser were recorded during each hour that sampling was conducted. Recorded activities were correlated with measured crossdrafts and capture efficiencies to determine how specific activities are related to crossdrafts and capture efficiencies.

Significant Findings

Measured crossdrafts ranged from near 0 to more than 2 fps. Measured workspace emission rates averaged 10.0 g/min and ranged from 0 to 254 g/min. Measured capture efficiencies averaged 0.83 and ranged from 0.08 to 1.00. Predicted capture efficiencies averaged 0.77 and ranged from 0.55 to 0.85.

Using overall averages, there appears to be reasonably good agreement between measured and predicted capture efficiency (0.83 measured vs. 0.77 predicted). However, examining the daily averages for each degreaser showed poor agreement between predicted and measured efficiency. This could be due to several factors: (1) turbulence was inadequately accounted for in the predictive model; (2) the effects of the cooling condenser were not considered; and (3) solvent was carried out of the degreaser to areas where the hood could not be expected to capture contaminants.

The ACGIH recommended flow rate for vapor degreasers is 50 cfm/ft^2 of tank surface.[1] The measured hood flow rates ranged from 72% to 162% of the recommended flow rate. The recommended flow rate appeared to be adequate for some conditions but inadequate for other conditions. An increase in

flow, above design recommendations, did not necessarily improve hood performance.

Smart, Safe Scaffolding

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Program Area: *Control Techniques*
Grant Number: *1 R43 OH03010-01*
Start & End Dates: *09/30/92 – 06/29/93*
Funding Level: *$0 ($49,650 Cum)*

Importance to Occupational Safety and Health

Over the past 25 years there have been more than 85 collapses of structures under construction that have been directly attributable to formwork failure. We have proposed to develop sensing systems and techniques applicable to the monitoring of construction site shoring and scaffolding. It is anticipated that this sensor network will provide significant information about the load distribution on shoring systems that is currently not available. This information will allow dangerous situations to be quickly identified so that corrective action can then be taken. Thus the risk of injury or loss of life at a construction site can be reduced, possibly leading to lower liability insurance costs. Furthermore, this information may also be used to formulate new construction codes that will further enhance construction work safety.

Objectives

The overall objective of this effort is the development of sensing systems and techniques applicable to the monitoring of construction site shoring and scaffolding. This work was demonstrated at our in–house laboratory facilities as well as at a "real–world" major construction site. The resultant sensor systems will have the inherent robustness and ease of use to be readily used on real construction sites while providing the dangerous situation identification necessary for increased construction site safety.

Methodology

This study, whose ultimate object is to design, develop, test, and evaluate methods to increase shoring and scaffolding safety at real–world construction sites, incorporates sensing system design along with laboratory and field testing. During the first phase of this study, a set of laboratory studies were undertaken to determine if unsafe loading conditions could be detected with scale model instrumented shoring systems. Three potentially dangerous loading conditions were examined: (1) overload; (2) soft footing; and (3) uplift. These situations were simulated using a test frame, strain–gage–based load cells, a data acquisition system, and model shoring. The next phase of the study involved taking shoring load measurements on a real construction site during a concrete pour and during the following cure cycle. Data were gathered using strain–gage–based load cells, a PC–based digital data acquisition system and a supplemental power supply. The field data were analyzed off–site.

Significant Findings

The laboratory studies indicated that overload, soft footing and uplift conditions could be detected on shoring systems with a proper interpretation of the load data. However, overload causes excessive loads to be measured, whereas soft footings involve an inability to carry a high load and uplift involves an initial load that reduces to zero. The identification of these situations requires the proper interpretation of the load data.

The field studies indicated that shoring loads could be readily monitored in the field. Construction sites are very rugged and required ruggedized equipment. The measured load data indicated that nothing out of the ordinary occurred at the site. The curing of the concrete was monitored from the load data by interpreting the loads with a simple exponentially–decaying load sharing model. The results calculated from the model agreed quite well with the measured data.

Publications

Huston DR, Ambrose TP, Fuhr PL, Devino E, Werner M: Construction Load Monitoring Using Instrumented Shoring. Proc. SPIE Conf. on Smart Materials and Structures, Orlando, FL, Paper No. 2191–48, in press, February, 1994

Ambrose TP, Huston DR, Fuhr PL, Devino E, Werner M: Shoring Systems for Construction Load Monitoring, Smart Materials and Structures, in press, 1993

Active Seat Suspension to Control Low Back Injuries

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Grant Number: *1 R43 OH03018-01*
Start & End Dates: *09/30/92 – 03/29/93*
Funding Level: *$0 ($32,613 Cum)*

Importance to Occupational Safety and Health

The operation of vehicles, e.g. trucks, has been demonstrated to be highly correlated with the occurrence of low back pain and herniated discs. Truck drivers and other vehicle operators typically report two to four times the number of low back pain problems and disabilities as the normal population. The economic and human costs of lower back injuries are enormous. Vehicle–related lower back injuries have been attributed in large part to vibration–induced stresses in the lumbar spine, especially vibration at the 4–5 Hz fundamental resonance of seated humans. The development and use of a seat suspension in trucks that suppresses most of the injury–causing vibrations would significantly reduce the number of back injuries and related disabilities. In addition, such a seat would have the added benefit of reducing operator fatigue and possibly accident rates.

Objectives

The overall objective of this work is to produce a vehicle seat suspension system that is capable of significantly reducing the vibrations experienced by a vehicle operator. Such a seat will be capable of preventing the occurrence and reoccurrence of vibration–induced fatigue and lower back injuries and disabilities. This seat must be relatively inexpensive and be capable of new or retrofit installation. The aim of this first phase of the project was to prove the feasibility of the concept.

Methodology

This study involved three major phases. These were:

1. A hydraulically damped commercially available truck seat was thoroughly tested on a vibration platform to analyze its response to a previously recorded truck cab input signal. Seat accelerations, velocities, and displacements were all recorded and analyzed to help in designing a semi–active suspension system.
2. A prototype was built based on the design from phase 1. This involved retrofitting a seat with a prototype computer controlled variable orifice hydraulic damper. A linear displacement transducer was fitted between the seat and base to provide relative position and velocity information for the control equation.
3. To test this seat a pseudo–human (spring–mass–dashpot system) with similar primary dynamic properties (resonance at approximately 4–5 Hz) was designed and built. This allowed for objective comparisons between this new actively controlled seat and existing passive seat suspension systems. Accelerometers were attached to the pseudo–human base and to the seat base in order to determine the vibration damping characteristics of the system. The seat was tested and compared in two modes; (1) damper orifice in active control, and (2) damper orifice fixed (passive) to provide approximately 0.7 critical damping.

Significant Findings

In the 4 to 5 Hz range the active seat reduced vibration to 77% of the amount for the passive seat. The fact that vibration at the human's natural frequency of 4–5 Hz was reduced as much as 23.3% is very important. Damage to the spine due to vibration most likely occurs from the work performed on the body by the kinetic energy from the vibration. Since kinetic energy is proportional to the square of acceleration, a reduction to 77% of the original acceleration is equivalent to a reduction to 59% of work done to the driver. This represents a significant improvement in the occupational health environment of the driver.

Evaluation of Respirators for Asbestos Fibers

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Importance to Occupational Safety and Health

Results from this research will provide quantitative information for determining the performance of respirators against asbestos and manmade fibers. The information can then be used as a basis to evaluate the current NIOSH procedures for certification of respirators for protecting workers exposed to fibers. Improved designs of the respirators and test procedures for NIOSH certification will help to reduce occupational exposures to asbestos and manmade fibers.

Objectives

The goal of this research is to quantify the performance of respirator filters used to protect workers in environments where they are at risk of exposure to asbestos and manmade fibers. Current OSHA guidelines require the use of respirators fitted with high efficiency filters. These filters must be approved under NIOSH certification criteria based on penetration tests using spherical aerosols. Fiber aerosols are known to have different aerodynamic behaviors than spherical particles and usually carry higher electrostatic charges. Because the carcinogenicities of asbestos and other fibers are known to be due, in part, to fiber dimensions, the efficiency of the respirator filters in relation to fiber dimension is very important. It is difficult to predict how fiber aerosols will penetrate respirator filters based on the NIOSH testing results using spherical particles.

The specific objectives of this study are: (1) to elucidate effects of fiber size, electrostatic charge, and flow rate on fiber aerosol penetration of filter cartridges, (2) to develop a mathematical model for predicting the penetration of fiber aerosols in respirator filters, and (3) to determine the fiber aerosol penetration through leaks in the face seal.

Methodology

Three asbestos fibers with mean diameters ranging from 0.04 to 0.5 μm and aspect ratios from 3 to 60 will be used. Both overall and size–specific penetration of fiber aerosols through filters will be determined. Based on size–specific fiber penetration information, the effects of particle diameter, length, and flow rate will be examined and the filtration mechanisms identified. We will then determine the dimensions of fibers that will most likely penetrate the respirator filter. We also hypothesize that electrostatic collection is the main reason for the inconsistent filter performance reported in the literature. This hypothesis will be tested by investigating the effects of electrostatic forces on fiber collection. Filtration models will be established to predict the penetration of fiber aerosols of given size distributions and electrostatic charges. Filter penetration efficiencies for spherical particles and fibers under these conditions will be compared to provide a scientific basis for evaluating the adequacy of current NIOSH guidelines, and for recommending possible improvements. The penetration of fiber aerosols through leaks in a respirator face seal will also be measured, and the effects of mass loading of fiber aerosols on flow resistance and fiber aerosol penetration will be determined. These studies can provide important information in determining respiratory fit factors for field use.

Significant Findings

1. The surface charge measurements on the respirator filters showed that some filters including those used in disposable respirators are charged to enhance the collection efficiency. Our data also showed that the surface charges decreased in a high–temperature and high–humidity environment and disappeared in a relatively short time. The deposition of spherical particles in the charged disposable filter was enhanced, as compared to the deposition of the same aerosol in the same filter after the charges were removed. On the other hand, for filter cartridges that did not carry electrostatic charges, collection efficiency was not enhanced. Our results suggested that the electrostatic charge in some filter cartridges was the major factor for increased collection efficiency. However, the efficiency enhancement due to these electrostatic charge effects may not be long–lasting when used in certain environments.
2. The mathematical filtration model for fiber and spherical aerosols showed increased filter

collection efficiency for elongated fibers due mainly to the interception mechanism. Because of the long axis, an elongated particle contacted the filter material and was collected. Our model showed that this interception effect increased with the aspect ratio. However, the interception effect was only effective for fiber aerosols with a volume equivalent diameter greater than 0.5 μm. For fibers smaller than 0.5 μm, the diffusion deposition mechanism dominates, and the filtration efficiency for fiber aerosols was not enhanced.

3. Preliminary results on the penetration of amosite fibers in a disposable filter showed that smaller and thinner fibers had higher penetration. We are analyzing the data. This preliminary result suggested that both the diameter and length distributions of a fiber aerosol change after filter penetration.

Publications

Chen BT, Irwin R, Cheng YS, Hoover MD, Yeh HC: Aerodynamic Behavior of Fiber and Disk-Like Particles in a Millikan Cell Apparatus. J Aerosol Science 24:181-195, 1993

Performance of Surgical Masks

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Importance to Occupational Safety and Health

Results of this study will extend our ability to protect both patients and operating teams from airborne and dispersed bloodborne pathogens. This concern is encouraging the examination of existing respiratory protective devices and the consideration of modifying devices used in industrial settings for use in health-care environments. About 6.9 million health care and other workers in the U.S. are at risk for blood contact at the worksite. The number at risk from aerosol transmission has not been accurately estimated; however, given the variance in mask collection efficiencies, the continued use of new technologies, and the potential for disease transmission, ascertaining the value of current mask protection is important.

Objectives

The objective of this research is to study the performance of masks currently used or considered for use in the health care industry. Specific aims are: (1) To study the currently used bacterial filtration efficiency test as to the particle size distribution of its spray. (2) To develop a method for simultaneously counting airborne test bacteria by physical and biological means on the masks being tested. This method is to be used to evaluate the collection efficiency of health care masks and to determine to what degree the collection efficiencies obtained with bacteria differ from those obtained by the use of inert, non-viable test particles currently used to evaluate industrial masks and respirators.

Methodology

Viable bacteria and inert particles are generated in the laboratory for testing a wide range of available masks. The masks are exposed in a test chamber specifically designed for studies of respiratory protective devices. The aerosols are analyzed physically by aerosol size spectrometry and biologically by sampling the bacteria into bioaerosol samplers. *Pseudomonas fluorescens* ATCC 13525 is used as the initial challenge bacterium. It is grown in tryptic soy agar at 25°C for 25 hours, washed and dispensed in deionized water. The size of this bacterium is approximately 0.5 μm in width and 1.5 μm in length, i.e. it is physically similar to the tuberculosis bacterium. The size-dependent penetration efficiencies of inert and biologically active test aerosols are compared with each other.

Significant Findings

Experiments with inert particles have shown a considerable range in collection efficiency values depending on the mask used. Penetration is highest for submicrometer-sized aerosols, approaching 100% for some masks used.Some industrially used dust-mist-fume respirators have less penetration than the best currently used surgical mask. However, in the presence of a large face-seal leak, the dust-mist-fume mask may not provide any more protection than a surgical mask with a lower filtration efficiency. Due to the higher pressure drop across the dust-mist-fume mask it may even perform worse than the surgical mask, because considerable aerosol

flow may be directed through the leak site. Thus, it is concluded that improvements in filtration efficiency in health care masks may necessitate quantitative fit testing to ensure proper fit of the mask to the health care worker's face.

Experiments with bacteria have shown that the penetration of bacteria is lower than that of inert, spherical corn oil. The difference is difficult to quantitate because it depends on the definition of particle size used for the complex shape of the bacterium. Further development of the test procedure is being performed before proceeding to the testing with bacteria of different physical and/or microbiological characteristics.

Publications

Weber A, Willeke K, Marchioni R, Myojo T, McKay R, Donnelly J, Liebhaber F: Aerosol Penetration and Leakage Characteristics of Masks used in the Health Care Industry. Am Journal Infection Control 21:167–173, 1993

Chen CC, Willeke K: Aerosol Penetration Through Surgical Masks. Am Journal Infection Control 20:177–184, 1992

Willeke K, Chen CC, Myojo T, Weber A, Krishnan U, Juozaitis A, Marchioni R, Lehtimaki M: Filtration, Loading and Faceseal Leakage Characteristics of Filtering Facepieces. J Aerosol Science 23:S749–S752, 1992

Factors Affecting Respirator Leak Sites and Shapes

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Importance to Occupational Safety and Health

Results of this study will expand our knowledge of where respirator faceseals leak and how those leak sites are related to such critical factors as facial dimensions, the brand of respirator, and if the 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 also 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 air flow streamlining patterns.

Methodology

The first four objectives will be accomplished by performing respirator fit tests on human subjects using an aerosol of an 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. 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

Activities completed to date include the selection and toxicological evaluation of an alternative fluorescent aerosol which could be nebulized in aqueous solutions, the construction and evaluation of a larger generation and exposure system, and mannequin tests at various inspiratory flow rates. Tests on human subjects have commenced and are partially complete.

Tinopol CBS–X has been used as the test agent in this study. This compound is water soluble, non–mutagenic, non–carcinogenic, and of low toxicity. It has a much higher fluorescent efficiency than the coumarin–type used in our previous studies,

and has provided better definition of leak sites and identification of streamlined air flow patterns. An aerosol generating and exposure system including three Liu nebulizers, aerosol conditioning system and exposure chamber been installed and evaluated. The aerosol size distribution has a MMAD of 1.2 μm and a geometric standard deviation of 1.4, and chamber concentration has been measured at ≈ 20 mg/m^3. Aerosol size distribution and concentration have been stable throughout the testing period.

Testing human subjects has progressed slowly because of a less than anticipated number of volunteers, loss of enrolled subjects from the study, and frequent turnover of research assistants. The tests on the mannequin showed that strong aerosol deposition patterns at low inspiratory flow rates did not persist at higher flow rates. This would indicate that air flow streamlining, and thus sampling bias, would be more likely to occur at low breathing rates characteristic of quantitative fit testing protocols.

Publications

Oestenstad RK, Graffeo JB: Determination of Respirator Fit by an Aerosol Method and a Negative Pressure Method. J Internat Soc Resper Prot, accepted for publication, 1993

Oestenstad RK, Perkins LL: An Assessment of Critical Anthropometric Dimensions for Predicting the Fit of a Half–Mask Respirator. Am Ind Hyg Assoc J 53:639–644, 1992

Oestenstad RK, Zwissler AM: A Comparison of Fit Provided by Natural and Silicone Rubber of the Same Brand of Half–Mask Respirator. Appl Occ Env Hyg 6:785–789, 1991

Oestenstad RK, Perkins JL, Rose VE: Identification of Faceseal Leak Sites on A Half–Mask Respirator. Am Ind Hyg Assoc J 51:280–284, 1990

Oestenstad RK, Dillon HK, Perkins LL: Distribution of Faceseal Leak Sites on A Half–Mask Respirator and Their Association with Facial Dimensions. Am Ind Hyg Assoc J 51:285–290, 1990

Rose JC, Oestenstad RK, Rose VE: A Comparison of Respirator Fit Factors Determined by Portable Nuclei Counting and Forward Light–Scattering Methods. Appl Occ Env Hyg 5:792–797, 1990

Adsorption of Vapor Mixtures onto Activated Carbon

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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 understand and 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 this investigation is to evaluate adsorption of organic vapor mixtures onto activated carbon. Experiments are designed to measure parameters associated with adsorption kinetics and equilibria. Binary vapor mixtures containing a variety of different polarities and functional groups at different humidities will be selected and tested.

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 a GC equipped with flame–ionization and photo–ionization detectors in series. The photo–ionization detector (PID) will be used with two different ionization potential lamps, 8.4 and 9.6 eV. Vapor pairs are selected such that the PID will respond to only one of the vapors in the mixture.

Significant Findings

The first phase of this investigation involved the development of the GC/two–detector system. The photo–ionization detector (PID) was installed on the GC. Different ionization potentials were evaluated in order to provide sufficient analytical sensitivity.

Vapor pairs to be used to evaluate component polarity effects have been selected and the adsorption system has been tested and calibrated.

Kinetic experiments using paired organic vapors onto activated carbon are complete. Experiments were designed to pair each of two test vapors, p–xylene and pyrrole, with polar and non–polar vapors (toluene and p–dichlorobenzene are non–polar and o–dichlorobenzene and p–fluorotoluene are polar). To account for any boiling point effects, each test vapor is also paired with vapors having a higher and a lower boiling point (the dichlorobenzene isomers have boiling points greater than p–xylene or pyrrole, while toluene and p–fluorotoluene have boiling points less than either test vapor). Comparison of the kinetic adsorption capacities of p–xylene and pyrrole for the different mixtures indicates that the adsorption space occupied by each vapor is reduced based on it's mole fraction in the mixture. The data do not indicate that there are any differences based on whether p–xylene and pyrrole are paired with polar or non–polar vapors. Furthermore the boiling point of the paired vapor does not seem to effect the kinetic adsorption capacity.

Collection of equilibrium adsorption data is 90% complete. Preliminary analysis indicates, similar to the kinetic experiments, that the overall adsorption space is conserved when isotherms are determined for paired vapors.

Aerosol Penetration Behavior of Respirator Valves

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Importance to Occupational Safety and Health

Properly fitted air purifying respirators must have functioning valves (exhalation and inhalation)in order to provide the protection expected. Inhalation valves open during inhalation and close on exhalation, thus ensuring that all expired air exits through the exhalation valve. The exhalation valve, which is the more important of the two in providing protection, closes during inhalation, thus ensuring that all inspired air passes through the filters before being breathed.

The adequate functioning of respirator valves is not often easy to evaluate. Respirators can be visually checked for malfunctioning valves; qualitative checks of their function are also possible. Neither of these methods is done often enough by respirator wearers, and neither guarantees adequate valve functioning. Only by quantitative measurement can the protection of a used respirator be determined, and this is rarely if ever done.

There is not, at present, any easy method by which valve replacement can be predicted. This research will lead to the development of an empirical model derived from experimental results which can be used to predict how often and when respirator valves must be replaced before they fail, given their particular use conditions. This model will be validated by comparison with measurements of used valve behavior.

Objectives

The objectives of this research include:

1. Evaluation of three respirator manufacturers' new exhalation and inhalation valves for particle size–related penetration as valves are stressed by a breathing cycle over an 8–hr period;

2. Evaluation of used valves for particle size–related penetration;
3. Comparison of predictions by an empirical model (developed from experimental data) to measurements of penetration made with used valves;
4. Evaluation of local companies' respirator maintenance practices, particularly as they relate to valve replacement.

Methodology

The experimental portion of this research will stress inhalation and exhalation valves using a breathing machine with humidified and heated exhalation air over an 8–hr period. Periodic measurements of aerosol penetration upstream and downstream of each valve type are made during the test period and recorded by computer, which also controls exhalation air conditions. Measurements of aerosol penetration will be made at several particle sizes, starting at 0.3 μm and extending to 1 μm. Two different work rates will be evaluated. The survey of respirator users has been completed by thirty local companies. Local companies have received new valves, which will used for a time equivalent to 8 hr before evaluation of particle size penetration in the laboratory. A model to describe particle–size related penetration for a given work rate over time will be developed. Model predictions will be compared with results of experiments with used valves.

Significant Findings

Of the 28 companies surveyed on respirator maintenance practices, 60% had workers wearing respirators on a daily basis for a range of aerosol and gas and vapor exposures. All but two of the companies had a formal, written respiratory protection program. In half of the companies the employee was responsible for inspecting the respirator on a daily basis prior to use, for maintaining the respirator as needed, and for replacing valves and filters or cartridges as needed. In all but three of the companies the person responsible for maintenance received formal training in repair methods. During inspection and maintenance, almost all companies indicated that inspection included a visual check of the harness, face piece, valves, and filters or cartridges; respirators were stored in a bag when not in use. In 60% of the companies cleaning and sanitization were accomplished by wiping or manually washing the respirator. A majority of the companies indicated the service life of their respirators as being about three to four years. Almost all companies indicated that worker training included inspection, cleaning and sanitization, maintenance, storage, and negative and positive pressure tests. Most companies indicated that these items were demonstrated by a trainer, while only half of the companies show videos and have workers practice the items during training Sessions.

For the experiments of valve leakage, two of four conditions have been evaluated to date: high and low flow with a small diameter (0.31 μm) aerosol. While the data have not been completely analyzed, initial evaluation shows that, under high flow conditions, the smaller aerosol may experience penetration up to 20% through exhalation valves and up to 5% through inhalation valves. Under low flow conditions penetration is much less, as expected. For exhalation valves penetration averages about 0.02% and for inhalation valves the 0.31 μm particles experience about 0.005% penetration. Experiments are presently underway for low and high flow conditions with a larger particle size (0.84 μm).

Lighter Compact Respirators For Toxic Vapor Protection

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Importance to Occupational Safety and Health

Lighter and more compact respirators can improve work place safety and health by providing greater comfort and ease of use. Worker acceptance and adherence to safety rules is enhanced when respirators are less cumbersome, easily and quickly donned and provide for unstrained breathing. The present research effort focuses on a system using two–way breathing through an absorbent medium so that valving may be eliminated to simplify and lighten the respirators. This system will also permit reuse of the absorbent elements by flushing and thus reduce cost.

Objectives

The goal of the research is to develop technology for lighter and more compact respirators using

alternating flow and absorbent materials insensitive to the presence of water vapor.

The project will identify suitable absorbent polymer and toxic gas pairs or groups that will allow reduction of the weight and size of respirator elements relative to activated charcoal elements in common use today. These materials will be used in a two–way flow breathing mode. Predictive codes for estimating the performance of various absorbent materials relative to selected toxic gases when incorporated in a filter design of specified geometry will be developed and validated. Experiments to assess performance will be conducted in a test apparatus simulating human breathing. Finally, an engineering study will be made to design two–way flow respirators and assess the practical issues of wearer comfort, face seal leakage and methods of mass production.

Methodology

A combined experimental and numerical modeling approach is being utilized to evaluate the influence of various parameters and materials on respirator performance. The predictive numerical code developed will compute mass and heat transfer in the absorbent materials using well grounded fundamental physical and chemical relations. Effects of temperature variation will be included where they affect the local thermal and mass diffusities as well as the solubility coefficients of the absorbents.

The experimental program provides for testing filter elements of reduced flow through area but of essentially full scale geometry otherwise. The test apparatus simulates the human breathing cycle and provides for concentration measurements using flame ionization detection in two–way oscillating flow with return flow matched in temperature and humidity to human breath.

Significant Findings

During the first phase of the research, the feasibility of the two–way flow concept was demonstrated. Experiments were conducted with a high boiling point vapor typical of many toxic vapors found in industrial work places in an experimental loop which simulates the human breathing cycle and includes a small section of an absorbent polymer. Measurements were made of the concentrations of the toxic gas simulant exiting the module as a function of time. Comparison of results for operation with two–way oscillatory flow with those of conventional one–way flow show a dramatic increase in the breakthrough time and a large decrease in the concentrations following breakthrough. These experiments demonstrated the feasibility of the new concept and its potential for superior performance relative to conventional respirators such as those using charcoal. Results of the numerical simulation model developed show similar significant improvements in respirator performance using two–way oscillatory flow over conventional one–way flow. A parametric study conducted with the numerical simulation model determined the influence of various factors such as partition coefficient, diffusivity and flow velocity on respirator performance.

Effects of 27 MHz Radiation on Somatic and Germ Cells

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Importance to Occupational Safety and Health

Current guidelines to protect workers from effects of radiofrequency radiation exposure 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. 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* to determine the validity of this premise.

Studies conducted to date provide firm evidence that these RF radiation frequencies affect cell mitotic activity under conditions that simulate occupational exposure. It has been determined that RF radiation directly affects cells in the absence of 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, permit testing hypotheses regarding the mechanisms of RF–induced alteration of mammalian somatic and germ cells.

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, permit testing hypotheses regarding the mechanisms of RF–induced alteration of mammalian somatic and germ cells.

Methodology

Cell suspensions are exposed for 2 hours to CW or PM 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 2h 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 >50W/kg suppressed cellular activity. Comparison 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 work place are known to involve radiation–induced heating in some instances.

Exposure of lymphocytes to either CW or PM 2450–MHz at SARs of 0.5– or 5 W/kg resulted in consistent suppression of lymphocyte proliferation 3 days postexposure. Mean suppression resulting from CW exposure was 8%. Exposure at 5 W/kg resulted in statistically significant suppression ($p=0.05$ for logarithmic transformed data), whereas suppression following exposure at 0.5 W/kg was not statistically significant. Exposure to PM 2450 MHz at SARs of either 0.5– or 5 W/kg resulted in statistically significant suppression (p values 0.0001 and 0.002, respectively). Exposure to PM 27–MHz RF radiation at 0.5– or 5 W/kg resulted in

statistically significant suppression with the exception of PM exposure at 0.5 W/kg.

Exposure of glioma to 0.5 or 5 W/kg CW or PM 27– or 2450–MHz RF radiation resulted in statistically significant, time–dependent increases in proliferation. Three days after exposure to CW or PM 2450–MHz RF radiation at 5 W/kg, glioma proliferation was increased 42– or 380%, respectively. Exposure to CW or PM 27–MHz resulted in statistically significant 14– or 50% increases in proliferation respectively. Three days following exposure of glioma to CW or PM 2450–MHz RF radiation at a SAR of 0.5 W/kg there was an 18% mean increase in proliferation, whereas CW or PM 27–MHz exposure, at this same SAR, caused a statistically significant (p=0.001) 119% mean increase in 3H–TdR uptake.

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 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. Recent studies of the effect of 27– or 2450–MHz RF radiation on human spermatozoa, using hamster ova penetration as the dependent variable indicate that human spermatozoa are less sensitive to RF exposure than mouse spermatozoa.

A novel helical coil RF exposure system has been designed and constructed to permit long–term exposure of mammalian cells *in vitro*. In contrast to other *in vitro* RF exposure systems which are limited to exposure durations of 2–4 hours, the helical coil system permits continuous exposure of mammalian cells to uniform RF fields under controlled conditions. This system was used to investigate the effect of a 24 h exposure of Chinese hamster ovary cells to 30 MHz RF radiation at a SAR of 0.5 W/kg. RF exposure caused a statistically significant increase in CHO cell proliferation.

A mathematical model has been used to calculate cellular level RF energy absorption in a mammalian cell model exposed to 27– or 2450 MHz RF radiation. Comparison of the distribution of absorbed energy in a simple cell model with absorption in a model incorporating a 2nm thick layer of bound (vicinal) water at the inner and outer membrane surfaces indicates significant frequency–dependent differences. Approximately 40 times greater absorption occurs in the bound water layer at 2450 MHz compared to 27 MHz. This finding suggests frequency–dependent differences in membrane related physiological processes.

Publications

Cleary SF: Biophysical Mechanisms of Interaction of Electromagnetic Fields. URSI Review of Radio Science, 1990–1992, in press, 1992

Cleary SF, Liu LM, Cao G: Cellular Effects of Extremely Low Frequency (ELF) Electromagnetic Fields. In: Charge and Field Effects in Biosystems, Boston, MA, Vol 3 Birkhauser, pp. 203–216, 1992

Cleary SF, Liu LM, Cao G: Radiofrequency Power Absorption in Mammalian Cells. In: Biological Effects and Safety Aspects of Nuclear Magnetic Resonance Imaging and Spectroscopy. Annals N.Y. Acad Science 649:166–175, 1992

Cao G, Liu LM, Cleary SF: Modified Method of Mammalian Cell Synchronization Improves Yield and Degree of Synchronization. Exptl Cell Res 193:405–410, 1991

Cleary SF: *In Vitro* Studies: Low Frequency Electromagnetic Fields. Proceedings of the Scientific Workshop on the Health Effects of Electromagnetic Radiation on Workers. U.S. DHHS, PHS, CDC, (NIOSH), Publication No. 91–11:17–43, 1991

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, N.Y., pp. 211–221, 1990

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

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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 manifestation. Such exposure(s) can bring about changes in plasma proteins in terms of their function, concentration, or covalent modification. These changes, which may be responsible for toxic effects, can 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

Covalent binding of acrolein to albumin

We have studied the covalent binding of acrolein to human serum albumin. Amino acid analysis showed four new ninhydrin positive peaks. These were identified as lysine and histidine adducts utilizing methods we developed earlier.

The adducts formed as a function of increasing concentration of acrolein was dose dependent between 1 to 10 mM range. The lowest concentration of acrolein used to quantitate the adducts was 1μ mM at an albumin concentration of 1 mg/ml. The effects of acrolein on the ultraviolet absorption and the biological function of the protein to bind fatty acid or bromocresol green were also studied. At acrolein concentrations of 2.5 to 10 mM, we observed an increased absorption at 280 nm by about 80%. This data suggest that more tyrosine and/or tryptophan residues were exposed due to the unfolding of the protein as a result of covalent modification of the lysyl and histidyl residues. In spite of significant numbers of modified lysyl and histidyl residues in albumin, the serum protein did not lose the ability to bind either palmitic acid or bromcresol green. Apparently, the alteration in the secondary or higher ordered structure (unfolding) of albumin did not affect its capacity to bind these ligands. These

studies indicate that even substantial covalent modification may not result in the loss of biological activity of albumin.

Rapid Quantitation of Acrolein and Crotonaldehyde Modified Albumin

We developed a rapid and sensitive method for the estimation of acrolein adduct of albumin which can subsequently be used as a marker of acrolein exposure.

In Vitro Studies: Human plasma albumin samples were incubated with increasing concentrations of acrolein (0.025 to 10 mM) at 37°C in 0.1 M phosphate buffer, pH 7.2, for 2 hr. After exhaustive dialysis, the modified protein was treated with [^{3}H]–NaBH4 to reduce the aldehyde adduct to corresponding alcohol. The radioactivity was measured after exhaustive dialysis and nmoles of carbonyl function/mg protein calculated. The response was found to be linear. This method is about four fold more sensitive compared to the amino acid analysis method in detecting covalent binding of acrolein to albumin. Although not as reactive, crotonaldehyde (a metabolite of butadiene) had a similar capacity to bind covalently with albumin as acrolein.

In Vitro Studies: Rats were treated with acrolein by gavage (13 mg kg^{-1}) and killed at 1,2,4, and 6 hr. Blood samples were collected and analyzed for adducts of plasma proteins and hemoglobin as described above. The adducts of both plasma proteins and hemoglobin were found to be significantly higher than in the controls.

The efficacy of this method needs to be established in humans before it can be used for molecular dosimetry.

Susceptibility to Degradation of Covalently Modified Albumin

In Vitro Studies: Albumin which was covalently modified by acrolein or crotonaldehyde as described above was incubated with elastase. Proteolysis in both cases occurred at a faster rate than with the native protein. Albumin treated with elastase degraded between 20 – 25% while covalently modified albumin with 5 mM acrolein or crotonaldehyde degraded 98 and 91% respectively. A dose response was observed between 0.025 – 5 mM range in both cases.

In Vitro Studies: Biosynthetically [^{3}H]–lysine labeled rat albumin was incubated with 5 mM acrolein in 0.1 M phosphate buffer pH 7.2 in order to prepare radioactively labeled protein adducts. The acrolein–adducted albumin and native albumin were injected intravenously into a group of rats. The disappearance of radioactivity was followed in plasma. In contrast to that of native albumin (t 1/2 of 12 hr), the corresponding estimated half–life of the adducted–protein was about 6 hr. Moreover, at the end of 33 hr after injection only 6.26% (5.5%, TCA–insoluble, and 0.9%, TCA–soluble) remained in the plasma vs. 20.4%, (19.4% TCA–insoluble; 1.1%, TCA–soluble) with native protein. Thirty–three hrs after the injection only 4.4% of the radioactive dose was associated with plasma albumin in the adducted protein, while 16.2% remained in the plasma when native albumin was used. The radioactivity data from the liver indicates that more degradation is occurring with the adducted protein (4.5%, in TCA–soluble function) than in the native protein (1.5%, TCA–soluble).

These studies show that chemically modified proteins may be degraded at faster rates than native proteins. Further studies are needed to substantiate this observation using several other protein adducts.

Publications

Trieff NM, Ficklen D, Gan J: *In Vitro* Inactivation of Glucose–6–Phosphate Dehydrogenase from Human Red Cells by Acrolein: A Possible Biomarker of Exposure. Toxicol Letters 69:121–127, 1993

Khan MF, Kaphalia BS, Boor PJ, Ansari GAS: Subchronic Toxicity of Aniline Hydrochloride in Rats. Arch Environ Contam Toxicol 24:368–374, 1993

Ahmad F, Kaphalia BS, Khan MF, Ansari GAS: Fatty Acid Anilides: A New Conjugation Pathway of Aniline. Biochem Arch 9:111–118, 1993

Awasthi S, Srivastava SK, Ahmad F, Ahmad H, Ansari GAS: Interactions of Glutathione S–Transferase–Λ with Ethacrynic Acid and Its Glutathione Conjugate. Biochim Biophys Acta 1164:173–178, 1993

Thakore K, Gan JC, Oandasan A, Ansari GAS: Quantitation of Blood Protein Adducts of Acrolein by Tritiated Bromohydride Reduction. Toxicol Methods 2:295–305, 1992

Kanz MF, Kaphalia L, Kaphalia BS, Romagnoli E, Ansari GAS: Methylene Dianiline: Acute Toxicity and Effect on Biliary Function. Toxicol Appl Pharmacol 117:88–97, 1992

Kaphalia BS, Ansari GAS: Covalent Binding of Ethylene Dibromide and Its Metabolites to Albumin. Toxicol Lett 62:221–230, 1992

Kaphalia BS, Bhat HK, Khan MF, Ansari GAS: Tissue Distribution of Monochloroacetic Acid and Its

Binding to Albumin in Rats. Toxicol Ind Hlth 8:53–61, 1992

Gan JC, Oandasan A, Ansari GAS: *In Vitro* Covalent Modification of Serum Albumin by Acrolein. Toxicologist 11:133, 1991 (Abstract #458); Chemosphere 23:939–947, 1991

Bhat HK, Asimakis GK, Ansari GAS: Uncoupling of Oxidative Phosphorylation in Rat Liver Mitochondria by Chloroethanols. FASEB J 5:A551, 1991 (Abstract #1950); Toxicol Lett 59:203–211, 1991

Bhat HK, Kanz MF, Campbell GA, Ansari GAS: Ninety-day Toxicity of Chloroacetic in Rats. Fund Appl Toxicology 17:240–253, 1991

Kanz MF, Bhat HK, Ansari GAS: Alterations in Hepatocellular Ultrastructure Following Oral Exposure to Chloroacetic Acids. Toxicologist 11:349, 1991 (Abstract #1371)

Gan JC, Ansari GAS: Inactivation of Plasma α_1–proteinase Inhibitor by Aldehydes Found in Cigarette Smoke. SAAS Bull Biochem Biotech 3:32–36, 1991

Gan JC, Ansari GAS: Inactivation of Plasma α_1–proteinase Inhibitor by Acrolein: Adduct Formation with Lysine and Histidine Residues. Mol Toxicol 2:137–145, 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

Ahmad H, Singh SV, Medh RD, Ansari GAS, Kurosky K, Awasthi YC: Glutathione S–transferases: Tissue Specific Expression in Lens, Cornea, and Retina. Arch Biochem Biophys 266:416–426, 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

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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, allows for the correction of biases in any dose–response relationships which are derived from the work. This study design has allowed us to detect elevated levels of SCEs at styrene concentrations below those which had heretofore been reported, even after adjustment for cigarette smoking. The development and application of methods for detecting styrene–7,8–oxide (SO) adducts of DNA (SO–DNA) and the blood proteins, hemoglobin (SO–Hb) and albumin (SO–Alb) 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 the dose of SO measured in blood samples, i.e., sister–chromatid exchanges (SCEs) in peripheral lymphocytes and the adducts, SO–Hb, SO–Alb 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.

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. Measurement of styrene in the exhaled air employed a new device which collects styrene from 3 L 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. Styrene glycol was measured in the blood by extraction followed by derivitization and gas chromatography with electron–capture detection. SO–DNA is being measured by a modification of the ^{32}P post–labeling technique developed in this study. A new technique has been developed for measuring SO–Hb and SO–Alb, which takes advantage of a metal catalyst (Raney–nickel) to selectively cleave SO–cysteine adducts to yield 1– and 2–phenylethanol, which are subsequently derivitized and measured by gas chromatography with negative–ion mass spectrometry.

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. A correlation matrix revealed that all of the biomarkers were significantly correlated with exposure to styrene. The strongest correlation with exposure to styrene was observed for exhaled air ($r=0.91$, $n=48$) followed by styrene in blood ($r=0.74$, $n=48$), styrene glycol in blood ($r=0.73$, $n=48$), SCEs ($r=0.35$, $n=46$), albumin adducts ($r=0.42$, $n=48$), and DNA adducts ($r=0.33$, $n=47$). All of these exposure–biomarker relationships were significant ($p<0.05$). Interestingly, a significant relationship was not found between hemoglobin adducts and exposure to styrene. The only biomarker which was found to be significantly correlated with SCEs was styrene in exhaled air ($r=0.45$, $n=46$). The correlations between SCEs and both exposure to styrene and styrene in exhaled air were still

significant after accounting for the number of cigarettes smoked per day by multiple regression analysis. This indicates that styrene exposure below 50 ppm, the current OSHA PEL, contributed to elevated SCEs; such findings of SCEs at these levels of styrene exposure have not been reported before.

We have successfully applied the ^{32}P postlabeling technique to *in vitro* modified samples of nucleosides, DNA, and cells and in samples of human DNA obtained from this study. The results clearly show that five SO–DNA adducts have been detected. Recent work 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. Application of the method to the human samples has confirmed the presence of the SO–N^2– adduct of guanine and of an as–yet–unknown adduct associated with styrene exposure.

The methods for measurement of SO–Hb and SO–Alb were first applied to samples of blood which had been modified with SO *in vitro*, and following administration of both SO and styrene to rats *in vivo*. The *in vivo* results suggest that only about 2% of the styrene dose was bioavailable as SO in the blood of rats. Application of the methods to the human samples has shown significant correlation with styrene exposure with SO–Alb but not with SO–Hb as noted above.

Publications

Rappaport SM, Symanski E, Kupper L: The Relationship Between Environmental Monitoring and Biological Markers in Exposure Assessment. Environ Health Perspectives, in press, 1994

Yager J, Paradisin W, Rappaport SM: Sister Chromatid Exchanges in Lymphocytes are Increased in Relation to Longitudinally Measured Occupational Exposure to Low Concentrations of Styrene. Mut Research, in press, 1993

Rappaport SM, Ting D, Jin ZL, Yeowell–O'Connell K, Waidyanatha S, McDonald T: Application of Raney Nickel To Measure Adducts of Styrene Oxide with Hemoglobin and Albumin. Chem Res Toxicol 6(2):238–244, 1993

Rappaport SM, Dionne L, Woodlee J, Yager J: The Relationship between Exposure to Styrene, Biomarkers of Exposure and Cytogenetic Response: (Abstract from the Proc of the 8th International Symposium of Epidemiology in Occupational Health, Paris, France, Sept. 10–12, 1991) Revue d'epidemiologie et de Sante Publique 40:S80–S81, 1992

Pongracz K, Kaur S, Burlingame AL, Bodell WJ: Identification of N^2–substituted 2′–deoxyguanosine–3′–phosphate Adducts Detected by ^{32}P–postlabeling pf Styrene–Oxide–treated DNA. Carcinogenesis 13(3):315–319, 1992

Compton PJE, Jensen RH, Bigbee WL, Langlois RG, Smith MT, Rappaport SM: Workers Exposed to Styrene Studied with the Glycophorin A Human Mutation Assay. Environmental Health Perspectives, in press, 1992

Rappaport SM, Kure E, Petreas M, Ting DT, Woodlee J: A Field Method for Measurement Vapors In Exhaled Air – Application To Styrene Exposure. Scand J Work Environ Health 17:195–204, 1991

Ting D, Smith MS, Doane–Setzer P, Rappaport SM: Analysis of Styrene Oxide–Globin Adducts Based Upon Reaction With Raney Nickel. Carcinogenesis 11:755–760, 1990

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, (eds. ML Mendelsohn, RJ Albertini), pp 3470–356, 1989

Bodell WJ, Pongracz SK, Burlingame AL, Liu SF, Rappaport SM: Investigation of Styrene Oxide–DNA Adducts and Their Detection in Workers Exposed To Styrene. In: Mutation and the Environment, Part C: Somatic and Heritable Mutation, Adduction, and Epidemiology, (eds. ML Mendelsohn, RJ Albertini), pp 271–282, 1989

Selvin S, Rappaport SM: A Note On The Estimation of The Mean From a Lognormal Distribution. Am Ind Hyg Assoc J 50:627–630, 1989

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

Hydrocarbon Exposure and Chronic Renal Disease

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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.

Because of an ever increasing number of end stage renal disease patients (ESRD)(i.e.– those 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 was to investigate the role of chronic exposure to hydrocarbons in causing chronic renal disease.

Methodology

This population–based case–control study utilized patients and controls identified from the major counties in Oklahoma. Cases included 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 included either a histologic diagnosis or the presence of unexplained proteinuria exceeding 2 gms/24 hrs. New cases diagnosed between January 1, 1985 and July 31, 1992 meeting these criteria were included in the study.

A general population–based control group matched to the cases by sex and age (±5 yrs) was selected from the same communities by a Random Digit Dialing technique.

A detailed questionnaire was administered to cases and controls. The questionnaire included 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.

A lifetime hydrocarbon exposure score was determined and expressed as average exposure in parts per million (PPM). This process included the following steps: (1) Development of a database of subjects' occupational histories which were given SIC (Standard Industrial Classification) and SOC (Standard Occupational Classification) codes by decade, (2) Formation of an expert panel of Industrial Hygienists to provide hydrocarbon exposure estimates for each SIC/SOC/decade combination, (3) Supplementation of exposure estimates by an extensive search of the literature and through the Occupational Safety and Health Administration Computerized Information System database located in Salt Lake City, and (4) Cross–matching of the SIC/SOC/decade combinations with the SIC/SOC/decade and length of employment for each job reported by each subject to determine the final estimate of lifetime hydrocarbon exposure.

Significant Findings

321 matched pairs were obtained. The subjects were mainly male (58%), white (79%) and married (71%) with about 54% never going to college. The cases were significantly less educated than controls and consisted of significantly more non–white subjects (Black, Hispanic, Native American and others). Significantly more controls drank diet soda and used artificial sweeteners. There was no difference in their smoking history and usage of coffee, tea, beer, wine and distilled spirits. The occurrence of a relative (parents, siblings, children, aunts, uncles or grandparents) with chronic renal disease was not significantly different between cases

and controls. Prescription and over–the–counter drug use was the same in both groups. Cases had significantly higher occurrence of high cholesterol, arteriosclerosis, heart attacks, fast heartbeats, angina, gout, frequent headaches and gallstones. Controls had a significantly higher occurrence of sinus conditions.

No significant difference was found between cases and controls regarding lifetime hydrocarbon exposure. No or low exposure (0–50 ppm) was seen in 51% of the cases and 52% of the controls. The exposure distribution was similar for all categories. Those with high exposure (500+) made up 8% of the cases and 9% of the controls. When matched pairs were compared, the case score was greater than the control in 122 pairs, but less than the control in 119 pairs. The case and control score were the same (if scores were within 10 ppm of each other they were considered equal) in 80 pairs. The odds ratio (using 100 ppm as the cutoff between exposure and no exposure) was significant when looking only at males over 30 years of age and for the subgroup of 92 cases with an unclassified diagnosis. When analyzing the subgroup of cases with creatinine levels over 4.0 mg/dl a significant OR (3.50) was also found. However, the unclassified subgroup consisted mostly of patients with high creatinine levels.

When analyzing the data by the extended Mantel–Haenszel test for matched analysis, a chi–square test which takes into account the actual dosage exposure for each pair, no significance was found overall or for any subgroups. No difference was found after controlling for possible confounding factors.

Biological Monitoring for Exposure to Coal Tar

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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 established. These methods require the collection of blood or tissue samples and are not practical for routine occupational monitoring. In this proposal, methods have been developed for the determination of exposure to benzo(a)pyrene (BP) by measurement of BP and its metabolites in urine. Since urine is much more readily collected than blood, this method should 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 its urinary excretion. An immunoassay for measurement of BP and its metabolites in urine was developed utilizing monoclonal antibodies recognizing these compounds. This new assay was validated in a model population, crude coal tar treated psoriasis patients and controls. Blood and urine were collected from patients and controls. Exposure to BP was also measured by a panel of previously developed assays including quantitation of white blood cell DNA adducts by immunoassay and [^{32}P] postlabeling and measurement of BP–albumin adducts and serum antibodies to BP–DNA adducts by immunoassay. Urines were analyzed for mutagens with the Salmonella typhimurium assay, for 1–hydroxypyrene by HPLC with fluorescence detection and with the new immunoassay developed in this project. The levels of different biological markers were correlated to each other and to exposure.

Methodology

To develop an immunoassay for the measurement of urinary BP, monoclonal antibodies were developed from animals immunized with BP covalently coupled to carrier protein and characterized in terms of sensitivity and specificity by competitive enzyme–linked immunosorbent assay (ELISA). An ELISA was developed for the sensitive detection of BP and its metabolites in urine. To validate the ELISA, urine from mice treated with radiolabeled BP was analyzed by ELISA and values correlated with those determined by radioactivity.

Blood and urine was collected from 50 crude coal tar treated psoriasis patients and 50 controls. Blood was separated into plasma, white blood cell and red blood cell fractions, and frozen. DNA was isolated from the white blood cells and adducts were determined by ELISA utilizing a previously developed antiserum recognizing BP diol epoxide modified DNA. This antiserum recognizes a number of structurally related PAH diol epoxide adducts and

thus provides a general marker of exposure to this class of chemicals. Total hydrophobic adducts were quantitated with the [^{32}P] postlabeling assay. BP protein adducts were measured in an ELISA with an antiserum recognizing these adducts. Plasma were 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 was measured by HPLC and mutagens determined with the Salmonella typhimurium mutagenesis assay. Creatinine levels were determined to standardize the data to urine concentration.

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 the adduct specific antiserum used in the ELISA 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

In a competitive ELISA 50% inhibition of antibody 4D5 binding is at 4 pmole of BP/well. There is significant crossreactivity with a number of BP metabolites and several other PAHs, including pyrene, 1–OH–pyrene 1–aminopyrene and 1–nitropyrene. To validate the ELISA, mice were treated with radiolabeled BP and urine collected. Metabolites, isolated by chromatography on Sep–pak C18 cartridges 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 is unknown. Thus, the assay will provide a relative measure of metabolites present.

The ELISA has been validated in humans by application to coal tar–treated psoriasis patients and controls. Urine samples were analyzed for the presence of PAH metabolites by ELISA, for 1–hydroxypyrene by HPLC with fluorescence detection and for mutagenicity by the *Salmonella typhimurium* mutagenesis assay. Urinary excretion of PAH metabolites, measured by competitive ELISA with a monoclonal antibody (4D5), were elevated in patients (mean 730±1370 μmol/mol creatinine) compared to untreated volunteers (110±90 μmol/mol creatinine, $p<0.0001$). 1–Hydroxypyrene was also elevated in patients (mean 547±928 μmol/mol creatinine) compared to volunteers (mean 0.14±0.17 μmol/mol creatinine, $p<0.0001$). While mutagenicity was elevated in patients compared to controls the difference was not statistically significant ($p=0.134$). There was a good correlation between the ELISA and 1–hydroxypyrene data ($r=0.717$, $p<0.0001$). These results demonstrate that the ELISA which can easily be carried out on large numbers of samples can detect exposure to PAH in treated patients.

PAH diol epoxide–DNA adducts in white blood cells, PAH–albumin adducts and measurement of serum levels of antibodies recognizing BP diol epoxide–DNA adducts were measured by ELISA. PAH–DNA adducts were elevated in patients (mean $6.77\pm12.05/10^8$) compared to controls ($4.90\pm8.81/10^8$). There was no difference in albumin adducts (mean 0.61±0.31 fmol/μg in patients and 0.63±0.30 fmol/μg in controls). About 30% of both patients and controls had measurable titer of antibodies recognizing BPDE–I–DNA adducts. In these studies, measurement of white blood cell DNA adducts was the most sensitive method for detecting exposure in coal tar treated psoriasis patients.

An immunofluorescence method has also been developed for the localization of PAH–DNA adducts in specific cell types. Initial application was to skin biopsies from treated patients and controls. Staining of fixed tissues with adduct specific antiserum was followed by fluorescein labeled secondary antiserum and indicated specific nuclear staining in biopsies of treated patients but not controls. Results agreed with quantitation of adducts by [^{32}P]postlabeling. The immunohistochemical method should be applicable to detection of adducts in biopsy material since small amounts of tissue are required.

The development of an immunoassay for PAH exposure which uses urine samples should greatly simplify biological monitoring of workplace exposure.

Publications

Santella RM, Nunes MG, Blaskovic R, Perera FP, Tang D, Beachman A, Lin JH, DeLeo V: Quantitation of Polycyclic Aromatic Hydrocarbons, 1–hydroxypyrene, And Mutagenicity in Urine of Coal Tar Treated Psoriasis Patients and Untreated Volunteers. Cancer Epi, Biomarkers & Prevention, in press, 1993

Santella RM, Perera FP, Zhang YJ, Chen CJ, Young TL: Immunologic Methods for Monitoring Carcinogen Exposure. European Optical Society/International Society for Optical Engineering, in press, 1993

Santella RM, Grinberg–Funes R, Perera FP, Zhang YJ, Chen CJ, Young TL: Molecular Epidemiology: Measurement of DNA Adducts. Advances in Cancer Research, in press, 1993

Santella RM, Gomes M, Zhang YJ, Young TL, Perera FP: Immunologic Methods for Detection of Human Exposure to Polycyclic Aromatic Hydrocarbons, Proceedings of Symposium on Health Risk Assessment and Surveillance in the Industrial Setting, Taipei, Taiwan, pp 81–94, 1992

Santella RM, Zhang YJ, Young TL, Li Y, Toor M, Lee BM, Stefanidis M, Warburton D, DeLeo V, Perera FP: Biological Monitoring of Exposure to Polycyclic Aromatic Hydrocarbons. In: Anticarcinogenesis and Radiation Protection: Strategies in Protection from Radiation and Cancer, (ed OF Nygaard), Plenum Press, New York, pp 155–169, 1991

Santella RM: DNA Adducts in Humans as Biomarkers of Exposure to Environmental and Occupational Carcinogens. Environ Carc Reviews C9(1):57–81, 1991

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 MD Waters) Plenum Publishing Corporation, New York, 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. J Skin Pharm 3:171–179, 1990

Selective Real-Time Detection of Olefin Gases and Vapors

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Importance to Occupational Safety and Health

This project has focused on the development of a prototype instrument employing coated surface–acoustic–wave (SAW) sensor technology for real–time measurement of several olefins and dienes that have been associated with carcinogenic, neurotoxic, and/or adverse–reproductive health effects. Due to the presence of other organic vapors in industrial settings where these chemicals are used, real–time measurement of these contaminants with current portable direct–reading instruments is often not possible. The sensitivity and selectivity provided by the proposed instrument should permit the collection of more accurate personal exposure data.

Objectives

The goal of this research has been to develop and perform laboratory performance testing of SAW sensors and associated instrumentation for monitoring several olefin and diene gases and vapors in the presence of common olefin and non–olefin industrial co–contaminants. The response of the SAW sensor, which is a function of change of mass that occurs in a chemically sensitive surface coating upon exposure to gas–phase analytes, has been tested for exposure to styrene, ethyl acrylate, acrylonitrile, 1,3–butadiene, vinyl chloride, and β–chloroprene, as well as other olefin and non–olefin gases and vapors. Selectivity for a given target olefin or diene has been achieved by coating the sensor with one of several novel trapping reagents.

Methodology

A large number of reagents have been synthesized and tested as sensor coatings for detection

of each of the target analytes. The reagents comprise Pt–olefin coordination compounds of the general formula trans–$PtCl_2$(amine)(olefin) designed to react, via substitution of the initially bound olefin, with certain olefin(s) and dienes. The steady–state rate of mass change accompanying the olefin substitution reaction is detected by the underlying SAW sensor, permitting real–time measurement of olefin/diene concentrations. By altering the electronic and steric properties of the ligands in the reagent, it has been possible to adjust the selectivity and sensitivity of the sensor. The sensor has been incorporated into a compact prototype instrument and tested in the laboratory over a range of operating conditions.

Significant Findings

Real–time measurement of styrene, ethyl acrylate, vinyl acetate and several butene isomers at low–ppm concentrations in the presence of each of several 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). In all cases post–exposure regeneration of the reagent has been possible by treatment with ethylene, *in situ*. A high degree of selectivity for the target olefins in the presence of other olefin gases and vapors was achieved and could be attributed to steric and electronic factors favoring reaction with the target olefins.

A systematic investigation of steric factors affecting the olefin–substitution reactions showed a remarkably high degree of selectivity for unhindered olefins. For example, ethyl acrylate could be monitored without interference from its more hindered isomers methylmethacrylate and methylcrotonate. Similarly, the response to styrene was about 8–10 times higher than that to α–methylstyrene and indene. Testing of various butene isomers showed that 1–butene could be monitored without interference from isobutylene. The effect thus appears to be quite general and similar selectivity would be expected for other less–hindered olefins in the presence of their more hindered structural analogues.

1,3–butadiene could not be measured with the Pt–ethylene reagent coating. However, use of the related reagent $PtCl_2$(1–hexene)(pyridine) permitted selective measurement of 1,3–butadiene with a limit of detection (LOD) of 100 ppb. In this case there is a 2–for–1 ligand exchange involved, with formation of the bridged Pt:butadiene complex $[PtCl_2(pyridine)]_2$(butadiene), which effectively amplifies the sensor response. No interference was observed from several industrially relevant non–olefin gases and vapors, and repeated regeneration of the reagent was possible by brief exposure to 1–hexene. Certain olefins could also be measured with this reagent, but only at concentrations higher than that of butadiene. For example, acrylonitrile could be detected above 2 ppm using the Pt–(1–hexene) reagent whereas it could not be measured using the corresponding Pt–ethylene reagent. Chloroprene could also be measured but only at concentrations above 100 ppm. Vinyl chloride gave measurable responses above about 30 ppm. Vinylidene chloride, dichloroethylene and trichloroethylene neither reacted nor interfered with the responses of the other analytes.

Replacing the pyridine ligand with 2,6–dimethylpyridine in the reagent precluded reaction with styrene but still allowed sensitive detection of acrylonitrile and butadiene. Use of a 60–MHz sensor instead of a 30–MHz sensor increased the sensitivity to butadiene by a factor of four (LOD = 24 ppb). Interestingly, ethyl acrylate did not react with the Pt–(1–hexene) reagent but it reacted quite rapidly with the Pt–ethylene reagent. Thus, it has been possible to achieve significant changes in the sensor response through subtle changes in the molecular design of the coating reagent.

A prototype battery–powered dual–SAW instrument has been designed and constructed. The instrument can provide real–time output of olefin and diene vapor concentrations as well as datalogging and coating–regeneration capabilities.

Publications

Zhang GZ, Zellers ET: The Influence of Substituent Electronic Factors on the Measurement of Gas Phase Olefins Using a Surface–Acoustic–Wave Oscillator Coated with trans–$PtCl_2$(olefin)(amine) Complexes. Analytica Chimica Acta 280:1–13, 1993

Zhang GZ, Zellers ET: A Coated Surface Acoustic Wave Sensor Employing A Reversible Mass Amplifying Ligand Substitution Reaction for Real–Time Measurement of 1,3–Butadiene at Low– and Sub–ppm Concentrations. Anal Chem 65:1340–1349, 1993

Zellers ET, Zhang GZ: Steric Factors Affecting the Discrimination of Isomeric and Structurally Related Olefin Gases and Vapors with a Reagent–Coated Surface Acoustic Wave Sensor. Anal Chem 64:1277–1284, 1992

Zellers ET, Patrash SJ, Zhang GZ: Selective Measurement of Organic Vapors Using SAW Sensors with Reactive or Sorptive Coatings: Steric, Electronic, and Solubility Factors. Proc 6th Int Conf Solid–State Sensors and Actuators Transducers '91, San Francisco, pp 998–1001, 1991

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

A Dichotomous Sampler for TRIG Aerosol and Vapor

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Importance to Occupational Safety and Health

The isocyanates are an important class of commercial chemicals used in the production of polyurethanes and certain pesticides. Exposure may result in occupational asthma, hypersensitivity pneumonitis, and accelerated decline in lung function. The compounds are highly reactive, and some have a high affinity for surfaces and relatively low vapor pressures at ambient temperatures. These properties result in a tendency for some isocyanates to partition into gaseous and particulate phases in the atmosphere. The physical state of the compound will affect its site of deposition/adsorption in the respiratory tract, as well as dictate the appropriate sampling techniques and engineering control methods. This project entails the development of a dichotomous sampler for total reactive isocyanate group (TRIG) vapor and particulate which will be used to characterize TRIG in workplace atmosphere in polyurethane foam plants and in isocyanate manufacturing plants. This work will result in a better understanding of the fundamental behavior of TRIG in the atmosphere and will offer a powerful tool for future studies of the toxicology of vapor and condensed phase isocyanate.

Objectives

A critical laboratory comparison of the selectivity, sensitivity, accuracy, and precision of analysis of the methoxy–phenylpiperazine (MOPIP), methyamino–methylanthracene (MAMA), and tryptamine (TRYP) methods will be performed using a series of model aliphatic and aromatic isocyanate monomers and oligomers. The best of these techniques will be adapted for use in an annular denuder for dichotomous sampling of condensed and vapor phase TRIG. After a thorough evaluation of the performance of the dichotomous sampler in the laboratory, it will be used in a survey of TRIG in representative workplace atmospheres, including isocyanate manufacture and flexible polyurethane foam production.

Methodology

Analytical derivatives of eleven isocyanate monomers with MAMA, MOPIP, and TRYP were synthesized in the laboratory. The isocyanates included methyl–, butyl–, phenyl–, benzyl–, o–tolyl–, and p–tolyl–isocyanate, and 1,6–hexamethylenediisocyanate, 2,4–toluenediisocyanate, 2,6–toluenediisocyanate, methylene–bis–(4,4'–cyclohexylisocyanate) (HMDI), and methylene–bis–(4,4'–phenylisocyanate) (MDI).

The analytical response of each of the derivatives was compared for consistency within derivatizing agent. Equimolar amounts of each derivative based on isocyanate content were analyzed by reversed–phase HPLC using three detection modes: MAMA derivatives were analyzed using fluorescence, and UV absorbance at two wavelengths; MOPIP derivatives were analyzed with electrochemical detection and with UV absorbance at two wavelengths; TRYP derivatives were analyzed with fluorescence, with electrochemical detection, and with UV absorbance. For each analysis, a response factor was calculated as the ratio of the integrated chromatographic peak area to the sample concentration in terms of isocyanate equivalence.

From the above work, MAMA was chosen as the derivatizing agent and was applied to quantitation of TRIG content in a series of oligomers of MDI and HDI in comparison to a reference titration procedure.

Testing of the dichotomous sampler for TRIG aerosol and vapor was also begun. The dichotomous sampler consisted of an impactor inlet, annular diffusional denuder (University Research Glassware) and treated filter, coated with derivatizing agent for isocyanates. Sampling of test atmospheres of vapor and condensation aerosol of MDI, vapors of HDI and TDI, and aerosols of HDI–biuret was accomplished with the sampler.

Significant Findings

Statistically significant intra-group differences were found across isocyanates for each of the three derivatizing agents and their three associated detection modes. The variabilities as measured by relative standard deviations of the mean response factors were as follows: MAMA derivatives; fluorescence, 55%; UV at 245 nm, 14%; UV at 370 nm, 8.6%; for MOPIP derivatives - electrochemical, 26%; UV at 242 nm, 50%; UV at 277 nm, 35%; for TRYP derivatives - electrochemical, 55%; fluorescence, 24%; UV at 280 nm, 24%. The MAMA derivatives were clearly the most consistent when detected by UV absorbance. The ratio of absorbance at 254 to that at 370 nm averaged 10.46 with a RSD of only 8.3%. These results led to the choice of MAMA for use in the TRIG technique. Assay of three oligomeric isocyanate materials based on MDI monomer using MAMA reagent resulted in average recovery of 100.6 ± 4.7% of TRIG content in comparison to a reference assay utilizing titration with di-n-butylamine. Several TRIG containing peaks were identified during chromatography, including the parent MDI monomer. Two HDI based oligomeric materials were also assayed resulting in a recovery of 103.2 ± 1.1%. HDI monomer and HDI-biuret were easily identified in these samples along with an unknown TRIG containing compound.

The dichotomous sampler clearly separated test atmospheres of MDI ranging from 24 to 355 $\mu g/m^3$ into vapor and aerosol fractions. Aerosols of MDI began to penetrate the diffusional denuder and collect on the backup filter at an MDI level of 75 $\mu g/m^3$, very near the saturated vapor pressure of MDI at 26°C. The overall performance of the device for both vapor and aerosol matched theoretical predictions closely.

Little penetration past the denuders was noted when sampling test atmospheres of HDI and TDI, indicating that these materials were in the vapor phase. HDI-biuret aerosols were found only on the impactor and back-up filter. Interestingly, the small amount of HDI monomer contained in the HDI-biuret was evenly distributed among the components of the dichotomous sampler, an indication of partitioning between aerosol and vapor phases.

Publications

Rando RJ, Poovey HG, Lefante JJ, Esmundo FR: Evaluation of 9-Methylamino-Methylanthracene as a Chemical Label for Total Reactive Isocyanate Group: A Comparison of Mono- and Di-Isocyanate Monomers. Journal of Liquid Chromatography, in press, 1993

Rando RJ, Poovey HG: Dichotomous Sampling of Vapor and Aerosol of Methylene-Bis-(Phenylisocyanate) [MDI] with an Annular Diffusional Denuder. American Industrial Hygiene Association Journal, accepted for publication, 1993

Theory and Evaluation of a Workplace OP-FTIR Monitor

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Importance to Occupational Safety and Health

This project has allowed advancement in the strategies, hardware, and software associated with the evaluation and use of remote sensing optical instrumentation in the workplace. Remote sensing systems need no sampling and pumping manifolds, are very fast, and can detect labile and polar air contaminants *in situ*. Quantitative results can be obtained for multi-component mixtures at concentrations of a fraction of the TLV. Full scale profiles of concentration fields of air contaminants can be determined. In addition, the presence of an active FTIR-air monitoring group allowed the concurrent development and evaluation of an FTIR system for biological monitoring of methanol via breath analysis.

Objectives

1. Design, construction, and pilot scale evaluation of open path-FTIR system hardware and software.
2. Completion of pilot scale test room, modeling of flow conditions, and strategy for optimal beam placement.
3. Field testing of fixed beam open path-FTIR system.
4. Modeling and pilot scale testing of "gamma" and time-series modeling concepts using fixed beam.
5. Field testing of "gamma" and time-series modeling concepts.

6. Design of system for rapid beam movement.
7. Modeling and pilot scale testing of "gamma", "optimbeam" and "tomography" concepts using rapid beam movement.
8. Field testing using system for rapid beam movement.

Methodology

Mathematical frameworks were developed for the relationship of beam averaged air contaminant concentrations to a critical volume of contaminated air that moves along with the worker as the worker moves through the workplace. The framework and software were also developed for optimizing the placement of a beam system for monitoring of exposures of workers in a concentration gradient. We then collaborated in the development of a OP–FTIR system with the capability of rapidly moving the beam. A new series of pilot experiments were then performed. Field tests are planned to parallel the pilot tests and evaluate the mathematical framework.

Significant Findings

1. During pilot scale evaluations, an open path–FTIR system, including newly designed hardware and software, operated in a manner suitable for use in the workplace.
2. A pilot scale test room was modeled and built for the open path–FTIR, and found to be suitable for evaluation of the instrument and for development of strategies for optimal beam placement in the workplace.
3. The open path–FTIR system was found to yield both quantitative and qualitative information regarding organic vapor and inorganic gas contaminants in workplace air during field testing at Abbott Pharmaceutical Laboratories.
4. Modeling strategies developed for this project have been found in pilot scale testing to be useful for determination of the relationship of open path–FTIR data to real time decisions of required levels of respiratory protection.
5. Software–based strategies have been developed and found to be useful for the analysis of data obtained from the OP–FTIR system in cases in which there is no source of clean air with which to obtain a background spectrum.
6. Time series analysis was found to be a useful method of determining when a statistically significant departure from normal airborne contaminant concentrations occurred during field testing at Monsanto Chemical Company.
7. Tomographic reconstruction of air contaminant profiles was demonstrated for full room–sized chambers.
8. Initial work performed in support of methanol exposure experiment resulted in reconsideration of ACGIH BEI, and in several publications (listed below).

Publications

Yost MG, et al.: Imaging Indoor Tracer–Gas Concentrations With Computed Tomography: Experimental Results With a Remote Sensing FTIR System. Amer Ind Hyg Assoc J, in press, 1994

Yost MG: Imaging Indoor Tracer–Gas Concentrations With Computed Tomography: Experimental Results With a Remote Sensing FTIR System. Amer Ind Hyg Assoc J, in press, 1994

Franzblau A, et al.: Absence of Formic Acid Accumulation in Urine Following Five Days of Occupational Methanol Exposure. Appl Occup Environ Hyg 8:883–888, 1993

Xiao HK, Levine SP: Application Of Computerized Differentiation Technique to Remote Sensing Fourier Transform Infrared Spectrometry for Analysis of Toxic Vapors. Anal Chem 65:2262–2269, 1993

Xiao H, Levine SP, Nowak J, Puskar M, Spear RC: Analysis of Organic Vapors in the Workplace by Remote Sensing Fourier Transform Infrared Spectroscopy. Am Ind Hyg Assoc J 54(9):545–556, 1993

Yost MG, Spear RC, Xiao HK, Levine SP: Comparative Testing of A Remote Sensing Optical System with Area Samplers in A Controlled Ventilation Chamber. Amer Ind Hyg Assoc J 53:611–616, 1992

Xiao HK, Levine SP, Nowak J, Puskar M, Spear R: Analysis of Organic Vapors in the Workplace by Remote Sensing Fourier Transform Infrared Spectroscopy. Amer Ind Hyg Assoc J, accepted, 1992

Wythoff B, et al.: Computer–Assisted IR Ident of Vapor–Phase Mixture Components. J Chem Info Comp Sci, 31:392–399, 1991

Xiao HK, Levine SP, Herget WF, D'Arcy JB, Spear R, Pritchett T: A Transportable Remote Sensing Infrared Air Monitoring System. Amer Ind Hyg Assoc J 52:449–457, 1991

Franzblau A, et al.: The Use of A Transportable FTIR Spectrometer for the Direct Measurement of Solvents in Breath & Ambient Air: Methanol. Amer Ind Hyg Assoc J 53:221–227, 1991

Levine SP, et al.: FTIR Least Squares Method for the Quantitative Analysis of Multi–Component Mixtures of Airborne Vapors. IN: Measurement of Toxic and Related Air Pollutants, Air Waste Manage. Assoc., Pittsburgh, PA, pp 895–900, 1990

Minimizing Work Schedule Disruption with Bright Light

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Importance to Occupational Safety and Health

It is generally acknowledged that almost three–quarters of the 20 million shift workers in the United States suffer from a variety of symptoms associated with the maladjustment of their circadian rhythms to an ever–changing work schedule. The cost of shift work due to accidents, loss of productivity, and increased health care demands is staggering. Recently, the aggregate social cost was estimated at approximately 70 billion dollars annually. Despite the magnitude of the problem, traditional approaches to reducing the impact of shift work have been largely unsuccessful. The traditional use of hypnotics to treat sleep disturbance in shift work populations is complicated by a number of factors, the most problematic of which are hangover effects on waking function and the potential for abuse. Attempts to implement behavioral strategies that address more closely the etiology of the disturbance have been largely unsuccessful due to compliance problems.

Objectives

In contrast, the use of bright light offers a safe and viable alternative to hypnosis. The approach offers rapid action without the drawbacks associated with pharmacological interventions. There is substantial evidence that exposure to bright light is effective in modifying both the phase and the amplitude of circadian rhythms, which in turn, can improve sleep quality and waking function. This knowledge has already been applied successfully in clinical circadian disorders, but surprisingly, it has not been used to address the problems associated with circadian adaptation to shift work. Because night shift workers are awake, and thus available, to receive light during intervals in which the most robust physiological effects have been demonstrated, they constitute an ideal population for such an approach.

Methodology

In previous studies, we have shown that two distinct components of bright light exposure are effective in alleviating sleep and/or performance deficits associated with rotating shift work. Timed exposure to a 4–hour pulse of very bright light (>6000 lux) on the first night of shift work facilitates adaptation by rapidly shifting circadian phase by up to five hours. Such re–setting of the biological clock improves daytime sleep quality and subsequent on–shift performance. In addition, exposure to ambient light of less intensity (approximately 1000 lux) throughout the night shift results in an immediate enhancement of alertness and performance efficiency. This effect is probably not the consequence of changes in the circadian timing system, but rather the result of a direct cortical activating effect of bright light exposure.

The current study seeks to examine the effects of a light regimen that combines these two components during a simulated shift work protocol. Because middle–aged shift workers suffer most from shift work maladaptation, it is these individuals who are likely to benefit most from the implementation of bright light interventions. As such, we are comparing rates of physiological and behavioral adaptation in 40 to 60 year old subjects in the combined bright light condition and a control conditions. It is expected that these important and necessary laboratory–based, simulated night shift studies will form the basis for subsequent investigations to evaluate the efficacy of such interventions in applied settings.

Significant Findings

Data acquisition is ongoing. The results reported here are from a group of subjects whose data have been fully analyzed. As such, the findings should be considered preliminary.

Bright light had the expected result on the circadian timing system. By the third night of shift work the Active group showed a mean delay in the course of body core temperature of over seven hours, whereas, the Control group exhibited a mean delay of less than four hours. Despite this, there was no significant difference between the Active and Control

groups in any measure of sleep quality following light exposure, with both groups exhibiting substantial reductions in the ability to sleep relative to Baseline. Post–hoc *t*-tests revealed significant reductions in sleep efficiency and significant increases in wakefulness after initial sleep onset. In addition, in the Active group, total sleep time declined by an hour. Similarly, analyses revealed that by the third night of shift work, no differences in performance were evident between the Active and Control subjects.

These results suggest that bright light treatment in middle–aged subjects may be less effective than equivalent interventions in younger subjects. It is essential that the issue of possible differential age effects be clarified if bright light interventions are to be of maximum benefit in the applied setting.

Publications

Campbell SS: Effects of Bright Light Exposure on Shift Work Adaptation in Middle–aged Subjects. Sleep Research, in press, 1994

Campbell SS, Dawson D and Zulley J: When The Human Circadian System Is Caught Napping: Evidence For Endogenous Rhythms Close To Twenty–four Hours. Sleep 16(7):638–640, 1993

Campbell SS: Alerting/activating Effects of Light. Sleep, in press, 1993

Campbell SS and Broughton RJ: Declining Body Temperature Prior To Sleep Initiation: Fluffing The Physiological Pillow? Chronobiology International, in press, 1993

Campbell SS: Effects of Sleep and Circadian Rhythms on Performance. In: Handbook of Human Performance, Volume 3, (eds A Smith, D Jones) New York, Academic Press, pp. 195–216, 1992

Measurement of Alkenyl/Epoxy DNA Adducts by GC-MS

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Importance to Occupational Safety and Health

DNA is an ultimate target in the body for carcinogenic and mutagenic chemicals. Measurements of DNA adducts therefore can help to sort out some of the uncertainties in exposure and risk assessment arising from exposure of individuals to chemicals. Our understanding of the biological significance of chemical damage to DNA is dependent on our ability to measure it.

Objectives

New analytical methodology is being developed to measure DNA adducts arising from occupational human exposure to ethylene, ethylene oxide, butadiene, styrene, and propene. These chemicals were selected since they are widely used and genotoxic. Also, they are anticipated to give similar types of DNA adducts.

Methodology

The proposed methodology basically comprises four steps: (1) isolate the DNA from a biological sample; (2) separate the DNA adducts from the bulk of the DNA; (3) derivatize the adducts with an electrophoric reagent; and (4) detect the electrophoric products by gas chromatography–electron capture negative ion–mass spectrometry (GC–ECNI–MS).

Significant Findings

For the N7 ethylene oxide adduct of guanine (N7–EO–G), we have developed a procedure that detects 1 picogram (5 femtomoles) of a standard of this adduct. We are now extending the method so that it will detect this adduct derived from a DNA sample.

Both solid phase extraction and HPLC are important sample cleanup techniques for the kind of methodology that we are developing. We compared their performance for the second derivatization reaction (a penafluorobenzylation) of the N7–EO–G and found that HPLC has a carryover problem. This problem was found to be due to the injector. We demonstrated that the use of two injectors overcomes the carryover problem.

We have begun work on the detection of the corresponding O^6–G ethylene oxide adduct. A novel chemical transformation reaction was required for this adduct that would retain the O^6–hydroxyethyl group. This has been achieved by converting the exocyclic amino to fluoro.

Some of the trace contamination in our methodology was found to derive from the Teflon liner and plastic cap employed to seal the reaction vial. This was overcome by introducing an all–glass vial. A patent application has been submitted by Northeastern University for this invention.

Our work is significant in two general respects. First, is the general significance of detecting DNA adducts in humans as biomonitors for exposure to chemicals. Second, is the broader methodological significance of the new chemical and physical techniques that we have developed to date for the N7–G and O^6–G ethylene oxide adducts.

Publications

Giese RW, Saha M, Abdel–Baky S, Allam K: Measuring DNA Adducts by GC–EC–MS: An Example of Trace Organic Analysis. Meth Enzymol, in press, 1993

Saha M, Giese RW: HPLC vs Solid Phase Extraction for Post–Derivatization Cleanup Prior to GC–ECNI–MS for N1,N3–Bis–(pentafluorobenzyl)–N7–(2–[pentafluorobenzyloxy}–ethyl)xanthine, A Product Derived from an Ethylene Oxide DNA Adduct. J Chromatogr 629:35–40, 1993

Saha M, Giese RW: Primary Contribution of the Injector to Carryover of a Trace Analyte in HPLC. J Chromatogr 631:161–163, 1993

Saha J, Saha M, Giese RW: 4–(Trifluoromethyl)–2,3,5,6–Tetrafluorobenzyl Bromide: A New Electrophoric Derivatizing Reagent. J Chromatogr 641:400–404, 1993

Chiu CS, Saha M, Abushamaa A, Giese RW: Chemical Transformation/Derivation of O^6–Methyl– and O^6–(Hydroxyethyl)guanune for Detection by GC–EC–MS. Anal Chem 65:3071–3075, 1993

Abdel–Baky S, Allam K, Giese RW: Derivatization in Trace Organic Analysis: Use of an All–Glass Conical Reaction Vial. Anal Chem 64:2882–2884, 1992

Abdel–Baky S, Giese RW: Gas Chromatography/Electron Capture Negative–Ion Mass Spectrometry at the Zeptomole Level. Anal Chem 63(24):2986–2989, 1991

Dosimetry for Workplace EMFs at Power-Line Frequencies

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Importance to Occupational Safety and Health

There is an increasing concern that electromagnetic fields (EMFs) at power frequencies may have health effects. A key research need, therefore, is to establish the mechanisms of bioeffects of these EMFs. An important aspect of this is to understand the coupling of the EMFs to the tissues in the human body. Knowledge in this area is relatively poor, since, in the past, only simple saline–filled and metal–coated idealized models have been used.

Objectives

The focus of our project is to obtain internal electric fields and induced current densities in heterogeneous, anatomically based models of the human body for a variety of worker exposure conditions encountered in occupational situations. Another objective is to develop two new instruments, namely the contact–current meter and the stored–energy meter, which may be used to assess the potential for shock and burns in the EMF workplace. Using an equivalent circuit as the human surrogate, the contact–current meter will measure the current that will flow for different conditions of contact such as finger or grasping contact, with or without rubber–soled shoes, and with or without safety

gloves. Likewise, the stored–energy meter will measure the open–circuit voltage and short–circuit current for various locations of possible worker contact, allowing an evaluation of the stored energy which is related to the possibility of spark discharge for transient contacts.

Methodology

The accomplishments of the 01 year of the project are as follows:

1. We have developed a new high–resolution model of the human body based on the magnetic resonance imaging scans of a male volunteer that were taken with a resolution of 3 mm along the height of the body and 1.875 mm for the cross–sectional planes. For this model we have incorporated the an isotropic conductivities of the various tissues such as the skeletal muscle and heart that are important for power–frequency EMFs. We have started to use this model to calculate induced electric–field and current–density distributions for exposure of the human body to incident vertical electric fields (up to 10 kV/m) and horizontal magnetic fields (up to 50 μT) associated with high–voltage power transmission and distribution lines.
2. We have developed computer graphical methods to obtain color pictures of the spatial variations of the calculated electric–field and current density distributions for the various cross sections of the body. Because of the fairly high electrical conductivity associated with regions of the cerebrospinal fluid (CSF), the highest current densities are calculated for these regions. We are also examining the current densities and E–fields induced for the region of the pineal gland, since alterations in the melanonin levels have been observed in laboratory animals exposed to EMFs at power frequencies.
3. We have started to calculate the induced currents in the human body for exposure to EMFs encountered in the workplace. To date we have calculated currents induced in the human arm and the body by the spatially varying magnetic fields of an electric drill and for linemen exposed to magnetic fields of high–voltage power transmission lines.
4. We have fabricated prototype contact current and stored energy meters to assess the potential for electrical and for hazardous transient spark discharges in the EMF workplace situations. The specifications for the contact–current meter are 0–50 mA and for the stored energy meter are 0–15 kV open circuit voltage and 0–50 mA short circuit current, respectively.

Significant Findings

1. The highest induced electric fields and current densities for a hand drill are for the front half of the right arm and for the sections of the torso that are in proximity to the hand drill. For a power drill with a maximum magnetic field of 500 μT the section–averaged current densities for the hand are as high as 2.5 mA/m2 and the highest local current densities are on the order of 8.5 mA/m2.

2. For linemen working on high–voltage power transmission lines the magnetic fields may be as high as S Gauss (500μT). Since these repairmen are often in a horizontal position parallel to the high–voltage line, they are subjected to these high magnetic fields that are fairly uniform over the extent of the body and are generally in the direction of arm to arm of the body. For such exposures we calculate a maximum induced current density of 1.0 mA/m2 and a maximum induced electric field of 7.3 mV/m.

We have surveyed the magnetic fields at the power generation facilities of a utility company. The highest magnetic fields on the order of 0.5 – 0.7 Gauss were found close to the output leads of the power generators. These magnetic fields were generally vertical and the highest magnetic fields occurred for the region of the floor above these leads or else underneath the leads on the primary side of the voltage step–up transformer. Using the millimeter resolution model of the human body we are presently calculating the induced current densities and electric fields for such occupational environments.

Biological Monitoring of Methanol Exposure

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Importance to Occupational Safety and Health

Methanol has been selected by the U.S. government as a primary candidate for promotion as an alternative automotive fuel. Usage as an automotive fuel would involve vastly greater opportunities for chronic low–level exposure of workers and consumers to methanol than have existed in the past. Human health effects related to chronic, low–level methanol exposure are largely unknown. There have been no human epidemiological studies focused on the effects of chronic low–level methanol exposure, and results of animal studies are difficult to extrapolate to humans because of significant differences in the metabolism and toxicity of methanol in most animal models. An essential component of any human epidemiological investigation of the effects of chronic low–level methanol exposure will be exposure assessment of subjects. Methanol is quite well absorbed via all major routes of exposure (gastrointestinal, inhalation, and dermal), so biological indicators of methanol exposure would provide more accurate assessment of the total absorbed dose, in comparison to routine measurements of the airborne concentration of methanol that are usually applied in the industrial setting. Although two approaches to biological monitoring of occupational methanol exposure have been endorsed by the ACGIH, the published data supporting these methods are limited, and in some areas, are contradicted by more recent reports. The data and analyses from this study will permit separate, quantitative examination of the major factors which are believed to influence biological indicators of methanol exposure in the occupational setting: airborne concentration of exposure; duration of exposure; level of pulmonary ventilation; and cutaneous exposure.

Objectives

The goal of this research is to identify valid, reproducible, and noninvasive methods for biologically monitoring occupational methanol exposure, and to assess quantitatively the impact of exercise and cutaneous methanol exposure on such indices. The underlying approach will be to perform a series of controlled experiments with volunteer subjects. Specific aims are to investigate the:

1. Use of formic acid (formate) in urine as a quantitative biological exposure indicator for exposure of humans to methanol via the inhalation route and via the cutaneous route;
2. Use of methanol in urine as a quantitative biological indicator for exposure of humans to methanol via the inhalation route and via the cutaneous route;
3. Use of methanol in end–expired (alveolar) air as a quantitative biological exposure indicator for exposure of humans to methanol via the inhalation route and via the cutaneous route;
4. Effect of exercise, as measured by the ventilation rate, on formic acid in urine, methanol in urine and methanol in end–expired air when humans are exposed to methanol via the inhalation route.

Methodology

The study will involve two sets of separate human experiments. In the first, paid volunteer subjects will undergo controlled exposures to methanol vapor in an exposure chamber. Each subject will have 10 separate chamber exposure sessions consisting of 5 different methanol exposure levels, and two levels of exercise/pulmonary ventilation. This is a complete block design experiment in that each subject will under each combination of `treatments' (5 levels of methanol exposure and 2 levels of exercise/pulmonary ventilation). Exposure sessions will last approximately 8 hours. Breath, blood and urine specimens will be collected before, during and after exposures. It is our goal to have 12 subjects complete this entire protocol. Methanol in urine and blood, and formic acid in urine will be assayed using gas chromatography. Methanol in breath will be measured using Fourier transform infrared spectroscopy. Minute ventilation at rest and during controlled exercise will be quantitated using standard pulmonary function methods.

The second set of experiments will address dermal methanol exposure and absorption. Each paid volunteer subject will have 5 separate exposure sessions consisting of different durations of controlled dermal exposure to methanol. Again, this is a complete block design experiment. Each level of

exposure is a 'treatment', and each subject will complete each 'treatment'. Dermal exposure of one hand to methanol will vary from zero to 8 minutes, and possibly up to 16 minutes. Baseline breath, blood and urine specimens will be collected before exposure begins, and will then be repeated at timed intervals for up to 8 hours following cessation of exposure. The goal is for 12 subjects to complete this entire protocol. Methanol in urine and blood, and formic acid in urine will be assayed using gas chromatography. Methanol in breath will be measured using Fourier transform infrared spectroscopy.

Significant Findings

The project started on 2/1/93. The focus of the first year of the project has been on writing and validating laboratory protocols for analyses of blood, urine and breath specimens, recruitment of volunteer subjects, and initiation of human experiments.

The first cycle of inhalation exposures was completed in October of 1993. This experiment involved 4 volunteer subjects. Exposure sessions generally involved all four subjects simultaneously. During each exposure session 2 subjects remained sedentary, and the other two subjects performed intermittent exercise on a bicycle ergometer. The minute ventilation of all subjects was quantitated both at rest and during exercise. The methanol exposures lasted approximately 8 hours. Subjects did not report any odor or irritant effects. Blood, urine and breath specimens were obtained before, during and immediately after cessation of exposure to methanol.

The first round of inhalation exposures has generated a large quantity of data. Preliminary analyses of these data indicate the following: (1) Methanol levels in urine and blood rapidly rise following exposure and approach a steady state level after an exposure period of approximately 5 hours; (2) Uptake and metabolic rates calculated from blood and urine data are in rough agreement with results of multicompartment models using parameters obtained from the literature; (3) concentrations of methanol in breath very rapidly approach equilibrium with chamber air, and do not reflect alveolar air, as demonstrated by very significant drops in concentrations of methanol in breath upon leaving the exposure chamber; (4) blood and urine concentrations of methanol appear roughly proportional to the methanol exposure level at steady-state; (5) inter-subject variability can be high, especially for methanol concentrations in urine and blood levels; (6) In some cases, e.g., low exposure experiments, several pre-exposure tests are needed to determine the absolute level and trend of background levels.

The first cycle of dermal methanol exposures was initiated in October of 1993, and will be completed in January of 1994. This experiment involves 4 subjects during each experimental session. Dermal exposures consist of putting one hand into a beaker of methanol (up to the distal wrist crease) for varying periods of time (from zero minutes up to 8 or 16 minutes). Two sessions (4 minutes and 8 minutes) have been completed. Blood, urine and breath specimens were/will be obtained before exposure, and at timed intervals up to 8 hours following cessation of exposure.

Publications

Franzblau A, Lee EW, Schreck RM, D'Arcy JB, Santrock J, Levine SP: Absence of Formic Acid Accumulation in Urine Following Five Days of Methanol Exposure. Applied Occup Environ Hyg, in press, 1993

Franzblau A: 1993-1994 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. ACGIH, Cincinnati, OH, 1993

Knowledge-Based Framework For Automating Hazop Analysis

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Importance to Occupational Safety and Health

Occupational safety and health hazards pose threats to an estimated 20 million workers in the manufacturing sector in the United States. Industrial statistics show that even though major catastrophies and disasters of chemical plants may be infrequent, minor accidents are very common, occurring on a day to day basis, resulting in many occupational injuries, illnesses, and costing the society billions of dollars every year [CMA, 1991]. For example, in 1983 alone over 3,000 job related deaths and an estimated 4.9 million job-related injuries and illnesses occurred [Bureau of Labor Statistics, 1985]. 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 [National Safety Council, 1985; McGraw–Hill Economics, 1985].

The occurrence of several catastrophic accidents in the refining and chemical industries during the 1980s has intensified public concern about process safety. The chemical industry, the federal government, and many state governments have responded to address these concerns in the form of new guidelines and requirements. The recently published final Occupational Safety and Health Administration (OSHA) standard on process safety management, Rule 29 CFR 1910.119 [OSHA, 1992], requires the use of a process hazards analysis (PHA) technique for the Identification of hazards for process systems containing toxic substances and/or flammable process materials above specified threshold quantities. OSHA estimates that such a process hazards analysis will be required at approximately 25,000 existing plant sites in the U.S. and for all the new ones that are built or retrofitted in the future [Freeman et. al., 1992]. At a typical plant site, five to ten different PHA studies will be needed to comply with the OSHA standard. This comprehensive mandatory review of process hazards will directly impact on the safety of about one million workers who are employed in the chemical industry, and many millions of people residing in the neighboring communities surrounding chemical plants [CMA, 1991]. It is estimated that about 100 million person–hours and 10 billion dollars might have to be spent using the current PHA approaches to meet this new regulation [Freeman et. al., 1992]. This project proposes to develop a novel computer–based framework that has a great potential to decrease this massive effort and also increase the productivity by providing for a fast, systematic, thorough, and detailed analysis of routine process hazards.

Objectives

HAZOP analysis is the study of systematically identifying every conceivable deviation, finding all the possible abnormal causes, and the adverse hazardous consequences of that deviation in a chemical plant (Kletz, 1991, McCluer and Whittle, 1992). This is a very difficult, labor–intensive and time–consuming process. Such an analysis is often carried out by a group of experts poring over the process P&IDs for weeks or months, applying a set of 'guide words' to the process variables associated with each process line and equipment, and finding the causes and consequences for those process variable deviations. This is a major labor– and knowledge intensive problem that can benefit from automation using Artificial Intelligence (AI) techniques. An automated HAZOP system can cut down on the time and effort involved in performing a HAZOP review, make the review more thorough, complete, and detailed, and minimize or eliminate human errors. The main goal of this proposal is to develop a knowledge–based system for automating certain aspects of HAZOP analysis and demonstrate its utility and performance on complex, industrial–scale, HAZOP case studies. Related subgoals involve the solution of various problems such as process knowledge representation, search and inference, HAZOP models development, system modification, validation and maintenance, graphical user interfaces, information overload

Methodology

The automation of HAZOP analysis demands the solution of a number of important problems as listed below:

- Ability to represent different types of knowledge such as if–then heuristics, cause–and–effect relationships, procedures, default reasoning, etc.
- Recognizing and representing that certain types of knowledge are the same for different process plants and certain other types of knowledge are unique to the process at hand
- Dealing with the propagation of causes and effects due to abnormal deviations through out the process plant, both in the forward and the reverse directions of material flow
- Handling loops and recycles in the plants
- Developing a convenient graphical user–interface that facilitates the use of the automated system for inputting knowledge, to perform HAZOPs on various sections of the plant, to generate explanations about what is going on, etc.
- Have interfaces to download information about the plant from P&ID diagrams and plant databases

In our proposed framework, we address all these problems and some other related issues by utilizing several novel techniques as listed below:

- A generalized object–oriented framework is used as the backbone of the system that will be able to represent and organize all kinds of knowledge including heuristics, causal models, procedures etc. This is a very powerful framework that will facilitate default reasonings, reasoning with composite objects, provide flexibility of control, facilitate inter–object communications etc.

- The problem of representing knowledge in HAZOP expert systems can be tackled if we divide the knowledge required for HAZOP into "process general" and "process specific" knowledge and allow for interactions between these two tiers of knowledge. This way, the general, basic knowledge required for performing HAZOP can be kept in the process general knowledge base, which remains fixed irrespective of the process plant under consideration and the process specific knowledge can be created separately for each process plant.
- The `process general' knowledge would be stored as a library of causal models that capture all the generic features of the process equipments and their behavior, represented as objects accessible through icons of the graphical user–interface.
- The `process specific' knowledge would consist of the type of the process materials, properties of process materials, the knowledge about the reactions and the type of the reactions (exothermic, endothermic, etc.), and the topology of the process units in the process plant under consideration. The process specific knowledge will be supplied n the user for each process plant.
- A sophisticated `message–passing' inference mechanism that provides for reasoning about the causes or abnormal deviations all the way to their root and to propagate the consequences all the way to the end. Thus, it can make the knowledge–based system reason forward and backward of material flow in the plant.
- An object–oriented graphical user–interface to attend to the needs of the developer and the user.

Significant Findings

None to date.

Statistical Issues For Compliance to Exposure Standards

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Importance to Occupational Safety and Health

NIOSH's Occupational Exposure Sampling Strategy Manual (Manual) contains industrial hygiene and statistical guidelines for sampling occupational environments and analyzing exposure data. The consequence of selecting high risk employees, namely those with maximum exposures, however, is not recognized in the analysis of this sampling for compliance to an environmental standard in a workplace. The application of extreme value theory will be explored.

Objectives

Three areas of statistical investigation are proposed: (1) to apply the theory of extreme values in the analysis of exposure measurements obtained by compliance sampling; (2) to examine alternative assumptions about the distribution of exposures by comparing a nonparametric procedure with fitting of a Burr XII distribution to exposure measurements; (3) to address the time series sampling of occupational environments by incorporating serial correlation into the analysis models.

Methodology

Applying the sampling theory of extreme values is the major objective. Specifically, the distribution of a maximum deals with the Manual's sampling of high risk employees and selection of the greatest exposure sites for evaluating ceiling standards. The basics of compliance sampling is to document the maximum exposures. The exact distribution of the maximum in samples from a specific distribution and the limiting Gumbel distribution of extremes are two aspects of the approach. And, knowing the number of workers/sites at lower exposures should be informative.

The concern for the distribution of exposure measurements will be addressed in two ways. First, a Bayesian nonparametric approach to compliance classification is provided and will be compared with parametric procedures. Second, an empirical feel for the relevance of normal, lognormal, Weibull and gamma distributions will be gained by plotting a variety of occupational exposure data on a moment–ratio diagram. Since the relevant portion of the skewness–kurtosis plane is covered by the Burr XII distribution, the fit of this distribution to a variety of exposure data will be explored.

The effect on compliance decisions of correlated exposures will also be examined. Short, partial–shift samples collected on a maximum risk employee during a single shift are likely to exhibit higher serial correlation than a sequence of 8–hour samples. First–order autoregressive models will appropriately increase estimates of variance, for example of mean exposures. Consequently, not incorporating autocorrelation may result in anti–conservative inferences.

Significant Findings

None to date.

Physiologic Sampler For Airborne Health Hazards

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Importance to Occupational Safety and Health

Inhalation exposures are typically assessed by personal breathing zone air monitoring using a constant flow sampling device. Although breathing zone sampling accounts for spatial and temporal variability in the air concentrations, it does not take into account spatial and temporal variability in the uptake of contaminants due to changes in pulmonary ventilation rate. This may well represent an important source of variability in exposure to inhalation hazards, since many common work tasks in construction generate exposures coupled with increased physical activity which alters breathing rates.

Furthermore, efforts to measure body burden of volatile organic compounds (VOC) have employed several methods, including breath sampling, to estimate the contaminant concentration in blood. Interpretation of these readings in complicated by the pharmacokinetics of VOC in humans, which can vary widely for different compounds. Single time–point measurements have limited value when attempting to estimate body burden from breath samples; multiple time course (washout) measurements however, can provide the basis for estimating decay rates and, in many cases, body burden. The difficulty with multiple measurements is the additional time they impose on workers, and increased analytical costs to employers. A simple and rapid breath analysis method, particularly one that employs a direct reading instrument and a repeated measures sampling strategy optimized to account for the wide range of VOC excretion rates, could provide a cost effective method for breath monitoring.

Objectives

The hypothesis of this project is that a personal air sample whose volume is proportional to the construction worker's inhaled air volume will yield a measure of inhalation exposure which is better correlated with the body burden, estimated through biological monitoring, than a constant flow air sample taken in the traditional way. If supported, this hypothesis will lead to significant improvement in the estimates of construction worker exposure to VOC using personal air sampling.

The specific aims of this study are:

1. to develop a physiologic sampling device, which samples at a rate proportional to an individual's pulmonary ventilation rate, and which can be worn as a free ranging personal monitor suitable for construction workers. Data on VOC concentration and exposure rate collected with this sampler from active subjects Wider laboratory conditions will be compared to conventional personal samples and to breath samples.
2. to use a novel instrument, the Rapid Exhaled Breath Analyzer (REBA), for monitoring expired air from solvent exposed construction workers. This direct reading instrument employs a customized Fourier Transform Infrared (FTIR) spectrometer to measure VOC mixtures in breath samples. Existing pharmacokinetic data for several target VOC will be used to develop a repeated measures sampling strategy aimed at

providing an estimate of body burden and hence absorbed dose, to be compared with the two measures of inhalation exposure.

3. to conduct a field pilot study using the physiologic sampler and REBA to analyze air and breath samples from solvent–exposed construction workers. The field pilot study will provide data to explore both the analytical sensitivity and sampling strategy that is most appropriate for VOC exposures in the construction industry.

Methodology

The sampling pump will use an input signal, derived from either heart rate or thoracic dimensions, to alter the air flow rate. Thus the amount of contaminant collected during the sampling period will be proportional to the mass inhaled by the worker. This contrasts with the traditional constant flow sampling methods which give a result proportional to the average ambient concentration of contaminant. The sampler will first be validated in laboratory experiments in which volunteers will wear the sampler while exercising on a bicycle at rates chosen to simulate work rates on construction jobs. Once validated in the controlled setting, the device will be placed on selected workers at local construction sites where exposure to paint solvents occurs. Performance of the sampler will be evaluated by taking breath samples from the workers at the start of the next shift to estimate absorbed dose. A high correlation between absorbed dose from breath samples and the physiologic sampler measurement will demonstrate the effectiveness of the new method.

Significant Findings

None to date.

Evaluation of Controls Protecting Lead-Exposed Workers

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Importance to Occupational Safety and Health

The study is a response to the persistent reports of elevated blood and air lead levels in bridge construction and maintenance activities and it represents an attempt to determine why high blood levels continue to occur despite government regulations and industry recommendations. It is designed to evaluate which work processes, controls, and practices contribute most to the lead overexposures and to determine whether and why the recommendations that have been made are or are not being implemented. Air and surface sampling as well as blood lead and changes in blood lead over a 2–week period will be done as measures of the effectiveness of the lead exposure control programs in use at each job site. The lead exposure control programs will be evaluated through examination of background on the company; the controls in place at the work site; the processes and work practices used on the work site; and the knowledge and attitudes of the workers themselves.

The investigators will provide the results of the blood lead tests to each study subject, and upon request, their physician. All blood test results will be reviewed by an occupational physician who will send a letter informing the individual of the health significance of the results and the recommended medical follow–up. Subjects will also be provided with a fact sheet describing the health effects of lead exposure.

Project participants will be provided a project summary at the end of the study. Information to be included will be summary blood lead levels, environmental sampling data, study conclusions, and recommendations. The final report, which will be completed at the end of the study, will be provided to appropriate agencies and institutions, e.g., OSHA and EPA.

This study is one of the first evaluations of structural steel paint abatement activities following the extension of OSHA's Lead Standard to the construction industry. The study, which uses innovative evaluation methods including the measurement of lead particle exposure in three particle size fractions, the creation of an ordinal index variables representing containment, ventilation, personal protection and similar variables using structured observations of work practices and the use of personal protective devices and control technologies, the use of blood lead observations over a defined interval, the use of ethnographic techniques (observation, questionnaires and semi-structured interviews) to assess worker and management awareness of lead poisoning issues associated with bridge repair work practices at each site, and the development of predictors of blood lead and air concentrations using industrial hygiene controls, work practice, training and company and worker attitude variables, will permit an early assessment of the impact of federal regulatory requirements and the barriers to optimal worker protection.

Objectives

The overall objective of this project is to determine why high blood levels continue to occur in bridge construction workers despite government regulations and industry recommendations. The project objective will be met through the following specific aims:

1. Perform a set of structured observations of work practices and the use of personal protective devices and control technologies at times coinciding with the exposure measurements. These observations will be combined into ordinal index variables representing containment, ventilation, personal protection and similar variables.
2. Measure lead particle exposure in three particle size fractions and perform surface wipe measurements for 150 Massachusetts bridge construction workers working in a variety of state Highway Department sites; there will be three to five exposure measurements during a two week study period at each site.
3. Per for n a project baseline blood lead on this group, followed by a second measurement 14 days later.
4. Use ethnographic techniques (observation, questionnaires and semi structured interviews) to assess management and worker awareness of lead poisoning issues associated with bridge repair work practices at each site.
5. Develop predictors of blood lead and air concentrations using industrial hygiene controls, work practice, training and company and worker attitude variables.

Methodology

This project is a cross-sectional survey of bridge repair and maintenance workers at work sites in Massachusetts. It is anticipated that project staff will visit fifteen work sites, and assess five workers at each site each year for two years. This will result in a total sample of 150 bridge workers in the survey. Workers will be interviewed in person using a questionnaire used in a previous study; they will also be asked to keep a work task diary during a two-week period. In addition, blood samples and air samples will be taken to determine individual-level exposures and biological markers of effect. Other information on environmental conditions and work practices will be gathered by project staff and used to construct a personal exposure score which will be used in the analysis. Blood lead levels at the beginning of the two week observation period will be compared with levels at the end. This is primarily to note whether biological measures changed significantly during the time period and, if so, to examine changes in job assignments or work tasks that might be associated with the changes. The mean blood levels for all workers involved in a particular task will be compared at the beginning and at the end of the two week observation period. The analysis of the data collected over the two year period will be focused on associations between specific work activities and environmental factors and blood lead levels and airborne lead levels for bridge repair and maintenance workers. The basic method of analysis will be analysis of variance (ANOVA) and analysis of covariance (ANCOVA).

Significant Findings

None to date.

Microsensor Array for the Identification of Organic Vapors

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Importance to Occupational Safety and Health

This project was motivated by the need for improved sensor technology in compact direct–reading industrial–hygiene monitoring instruments for organic vapors. The high–cost, complexity, and/or poor selectivity of currently available direct–reading instruments preclude their use in routine personal exposure monitoring applications. Instruments employing SAW sensor arrays can provide rapid identification and quantification of a wide range of organic vapors of occupational health concern. The small size, versatility, and potential low cost of instruments based on SAW sensor technology promise improvements in the quality and quantity of data used to guide industrial hygiene exposure assessment and control efforts.

Objectives

This project has entailed a series of laboratory investigations of several performance parameters relevant to the deployment of instrumentation employing microfabricated surface–acoustic–wave (SAW) chemical sensor arrays for the measurement of organic solvent vapors in the occupational environment. The primary goal was to develop arrays of coated SAW sensors and pattern recognition methodologies to provide optimal sensitivity and selectivity for each of a wide range of organic vapors when present alone or in simple mixtures. In addition, semi–empirical predictive models of sensor responses were developed and the effects of environmental variables were characterized.

Methodology

The prototype instrument tested here included an array of four 158–MHz quartz SAW oscillators, each having approximate dimensions 0.5 cm^2. The instrument was not optimized for field use. Sensitivity to organic vapors was achieved by coating each of the sensors with a polymer or high–boiling liquid into which the vapors would reversibly partition: vapor sorption increases the mass and decreases the elastic stiffness of the surface coating film which causes a commensurate shift in the oscillation frequency of the sensor. Responses from SAW sensors overlayed with each of 16 different isotropic polymer coatings were collected following exposure to each of up to 40 organic vapors representing 12 different chemical classes. Various binary vapor mixtures were also tested. Certain coatings were found to be unstable and were eliminated from further consideration. Response patterns for each vapor or vapor mixture were obtained from all possible combinations of four coated sensors in the data set. Pattern recognition analysis was used to decode the multidimensional sensor array output and to select optimal sets of coated sensors for inclusion in the array for a given set of vapor analytes. Subsets of coated sensors and vapors were examined at different temperatures and relative humidities. Semi–empirical predictive sensor response models were also developed.

Significant Findings

Limits of detection were typically in the range of 1–80 ppm. Lower detection limits were generally obtained for the less volatile and more polar vapors. Measurement of most vapors below their ACGIH–TLV values was demonstrated. Recent improvements in SAW sensor design promise a reduction in detection limits of up to an order of magnitude. Sensor responses are dependent on temperature and, in certain cases, on relative humidity, indicating a need for compensation for, or control of, these variables. The sensors provide stable, reproducible responses for periods of at least eight months indicating minimal recalibration requirements.

A new pattern recognition method was developed for determining which coated sensors would maximize the selectivity and accuracy of detection of a given subset of vapor contaminants. Using this method in conjunction with a Monte Carlo simulation procedure, optimal subsets of coated sensors can be selected for inclusion in the array for any potential exposure situations. This approach to coating selection allows the assessment of sensor array performance in terms of correct vapor identification rates, quantification accuracy, and the influence of

potential interferences. With proper design, a single array can identify and quantify a wide range of different vapors when present individually or in simple mixtures.

Also developed during this project were several predictive models of sensor responses. Models based on vapor boiling points, coating/vapor solubility parameters, and coating/vapor solvation parameters used in conjunction with linear solvation energy relationships (LSER) were examined. The LSER model provided the most accurate correlation of modeled and experimental responses. Use of this model, together with the pattern recognition method described above permits the selection of optimal coatings and the estimation of array performance without the need for experimental calibrations.

These investigations showed that with a simple four–sensor array it is possible to identify and quantify each of a large number of organic vapors. Using optimized arrays, errors in identification are generally restricted to cases of mixtures where one component is present at concentrations near the detection limit and the mixture is identified as the dominant component alone. In addition, while surprisingly good discrimination between vapors both between and within chemical classes is possible, identification errors are observed for some vapors of similar structure. A preliminary investigation of liquid crystals as sensor coatings shows that this class of sensor coatings can enhance discrimination by virtue of subtle size and shape differences between otherwise similar (e.g., isomeric) vapors.

Publications

Patrash SJ, Zellers ET: An Investigation of Nematic Liquid Crystals as Surface Acoustic Wave Sensor Coatings for Discrimination Between Isomeric Aromatic Vapors. Analytica Chimica Acta, in press, 1993

Zellers ET, Pan TS, Patrash SJ, Han M, Batterman SA: Extended Disjoint Principal–Components Regression Analysis of SAW Vapor Sensor–Array Responses. Sensors and Actuators B 12(2):123–133, 1993

Patrash SJ, Zellers ET: Characterization of Polymeric Surface Acoustic Wave Sensor Coatings and Semiempirical Models of Sensor Responses to Organic Vapors. Anal Chem 65:2055–2066, 1993

Zellers ET, Patrash SJ, Zhang G: Selective Measurement of Organic Vapors Using SAW Sensors with Reactive or Sorptive Coatings: Steric, Electronic, and Solubility Factors. Proc 6th Int Conf Solid–State Sensors and Actuators – Transducer '91, San Francisco, pp 998–1001, June 1991

Optical Remote Sensing and Computed Tomography in Industrial Hygiene

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Importance to Occupational Safety and Health

Current methods for sampling and evaluating air concentrations of gases and vapors involve the use of integrated samplers or direct–reading instruments. The integrated sampling devices result in a time–weighted average result; fluctuations in concentrations are smoothed out resulting in poor temporal resolution of chemical concentrations. Although direct–reading instruments do not suffer from the temporal resolution problem, both methods are essentially point samplers and give poor spatial resolution of concentrations. Currently, there are no methods which can give both good spatial and good temporal resolutions of chemical concentrations for an area.

This research is investigating an air sampling and evaluation system that does not suffer from these problems. This method combines the techniques of optical remote sensing with computed tomography to determine the concentration distribution of a gas or vapor in a workplace. Chemicals would be detected over large areas remotely, non–invasively, and in real–time; the system would produce a topographical map of the distribution with both good spatial and good temporal resolution.

The optical remote sensing/computed tomography system would have wide application in industrial hygiene work. It could be used for routine monitoring of chemical vapors in a workplace, evaluation of ventilation systems by using tracer gases or monitoring airflow of chemicals, and detection of leaks from an operation.

Objectives

This research proposes to combine the techniques of optical remote sensing with computed tomography to determine the concentration distribution of a gas or vapor in a room, non-invasively and in real-time. The aims of the research are to develop and test theoretical designs for a remote sensing/computed tomography system in a workplace, and to evaluate them by constructing a prototype system.

Methodology

Specific goals of this research involve: (1) designing and testing feasible optical remote sensing geometries for the placement of light sources and detectors in a room; (2) developing image reconstruction algorithms and computer code to produce the maps of concentration distributions; and (3) validating the remote sensing/computed tomography system in a controlled chamber and using a calibration cell using a tracer gas to create test concentrations.

Successful completion of this work will demonstrate the feasibility of the proposed technique. The next step in the research program, following completion of the work proposed here, will be field evaluation of the system.

Significant Findings

A systematic method has been developed to compare the effectiveness of different algorithms, and different optical remote sensing geometries for tomographically reconstructing chemical concentrations in air from an optical remote sensing system. The underlying assumption is that the performance of an algorithm, and usefulness of a configuration cannot be accurately assessed without thorough testing using a wide variety of possible concentration maps under ideal and non-ideal sampling conditions. Four different algorithms, and ten configurations have been evaluated in numerical studies using 120 different test concentration maps, and six different sampling conditions.

The algebraic reconstruction algorithms, ART and ART3 were found to be superior to other algorithms tested. In terms of resolution, the equal angle configuration is optimal because it floods the room with contiguous parallel rays; however, it is hardware intensive. An alternative configuration, that provides reasonable reconstructions, but introduces more artifacts, is the scan configuration. Four sources, one in each corner must be used for adequate reconstructions. Reconstruction quality was related to the number of detectors, the location of detectors in the room, and the complexity of the test concentration maps.

The performance of an infrared optical remote sensing device was evaluated using an exposure chamber, and a five-compartment calibration cell placed directly in the optical path. Open-path measurements of SF_6 were compared with point sample measurements taken along the beam and analyzed using a GC-ECD or a MIRAN IR spectrophotometer. The open-path measurements were in close agreement, within 10-12%, with path-averaged concentrations calculated from the point samples. There was no significant difference found in measurement accuracy for a variety of path lengths, between the experiments performed using the chamber or calibration cell, homogeneous or heterogeneous tracer gas concentrations, and single or reflected-beam configurations.

Publications

Todd LA, Ramachandran: Evaluation of Algorithms for Tomographic Reconstruction of Chemicals in Indoor Air. AIHA Journal, in press, 1993

Todd LA: Optical Remote Sensing/Computed Tomography Systems for Workplace Exposure Assessments. Proceedings Optical Remote Sensing: Applications to Environmental and Industrial Safety Problems SP-81:356-360, 1992

Todd LA: Optical Remote Sensing/Computed Tomography Beam Geometries for Monitoring Workplace Gases and Vapors. Proceedings Optical Remote Sensing: Applications to Environmental and Industrial Safety Problems, SP-81:390-393, 1992

Measurement Errors in Occupational Epidemiology

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Importance to Occupational Safety and Health

Nearly all occupational studies face problems measuring the exposure variable. Although other types of epidemiology are also faced with this problem, the necessity of retrospective exposure assessment in most cohort studies and the cost of detailed personal exposure sampling even in prospective and cross–sectional studies makes this a particularly difficult attribute of occupational safety and health research. It is quite possible that many occupational studies which have been interpreted as negative have in fact failed to detect important exposure–response relationships due to substantial exposure measurement error or misclassification. I propose to contribute to a resolution of these problems through the development of statistical methods to adjust point and interval estimates of relative risk for bias due to measurement error. By illustrating these procedures with examples from important occupational data sets, it is hoped that the use of these methods of design and analysis will become standard practice in occupational epidemiology.

Objectives

1. To develop new simple measurement error methods for 1) retrospective cohort studies, 2) case–control studies, and 3) cross–sectional studies of occupational exposure–disease relationships
2. To illustrate the use of these methods through the analysis of important occupational data sets, including: (a) the GM/UAW study of respiratory and digestive cancer mortality and cumulative machining fluids exposure, (b) the New Mexico uranium miners' study of exposure to radon progeny and lung cancer mortality, (c) the GM/UAW study of acute respiratory effects and components of current machining fluids exposure, and (d) the ACE study of between health and occupational exposure to anti–cancer drugs
3. To develop user–friendly computer software to implement those methods which appear to be most useful in practical settings.

Methodology

All methods require a small validation substudy in which the usual method of exposure assessment is validated against a more accurate method. Then, a measurement error model is developed empirically from these data. This is used explicitly in maximum likelihoods methods to obtain an unbiased estimate of effect, which takes into account measurement error as modeled through the validation substudy. Measurement error models appropriate for cumulative exposure variables are a special focus of this research.

Significant Findings

Current work involves investigating parametric full maximum likelihood methods for a constant prevalence ratio model with a realistic exposure measurement error model, such as based on the gamma or log–normal distribution. It appears that the gamma family of distributions for X|Z fit these data well, and leads to a closed form likelihood for the main study distribution of symptom prevalence conditional on exposure. Using the validation study data, we fit a gamma measurement error model to the distribution of X|Z with parameters $\mu(Z,U)=a_\mu + b_\mu Z + \mathbf{c}_\mu'\mathbf{U}_\mu$ for the mean of X|Z,U and with shape parameter $\nu(Z,U)=a\nu + b_\nu Z + \mathbf{c}_\nu'\mathbf{U}_\nu$, where $\mathbf{U}_\mu$ and $\mathbf{U}_\nu$ are arbitary dimensional vectors of covariates which may or may not be the same. Using a constant prevalence ratio model, $\Pr(D=1) = \exp\{\alpha + \beta Z + \boldsymbol{\gamma}'\mathbf{U}_\gamma\}$ for symptom prevalence, where $\mathbf{U}_\gamma$ is an arbitrary dimensional vector of covariates which may or may not be idential to $\mathbf{U}_\mu$ and $\mathbf{U}_\nu$ used for the measurement error model, we derive the distribution $\Pr(D=1|Z,U) = \int \Pr(D=1|X,\mathbf{U}_\gamma)\, f(X|Z,\mathbf{U}_\mu, \mathbf{U}_\nu U)\, dx =$

$$e^{\alpha+\boldsymbol{\gamma}'\mathbf{U}_\gamma}\left[\frac{\nu(Z,U_\nu)}{\nu(Z,U_\nu)-\mu(Z,U_\mu)\,\beta_1}\right]^{\nu(Z,U_\nu)}$$

We then maximize the likelihood

$$L(\beta,\,\theta) = \sum_1^{n_1} h(D|Z;\,\beta,\theta) + \sum_1^{n_2} f(D|X;\,\beta)$$

and obtain an estimate of the variance–covariance of the parameter estimates as the inverse of the observed information matrix at the maximum likelihood estimates.

Detailed analysis of two symptoms, chest pain (CHEST) and loss of appetite (APPETITE), has progressed nicely. In this analysis, the exposure of interest was defined as number of doses of antineoplastics mixed per week. It was self–reported by memory (Z) in the main study, and measured through a 1–2 week written log (X) in the validation study. The correlation between these two methods of measurement was estimated at 0.42. For the purposes of illustration, I present the results of the analysis for chest pain. Using stepwise regression techniques and likelihood ratio testing procedures, we discovered empirically that $\mathbf{U}_\mu$ = current smoking status, $\mathbf{U}_\nu$ = age, and $\mathbf{U}_\gamma$ = (stress, body mass index and age). With these model covariates, we then

estimated the effect of number of drugs mixed per week using several strategies and compared the results.

The relationship between the prevalence of chest pain, and number of doses of anti-neoplastics mixed per week, among hospital pharmacists and pharmacists' assistants

Methodology	(X 10^3)		POR [1 SD(X) Δ^1] (95% CI)	p-value, Wald test	p-value, LRT[2]
uncorrected logistic regression	1.60	0.807	1.02 (1.00-1.04)	0.048	n/a
Rosner *et al.*[3] correction	10.84	6.4	1.16 (0.98-1.37)	0.093	n/a
uncorrected constant prevalence ratio model	1.00	0.745	1.01 (0.99-1.03)	0.180	0.033
constant prevalence ratio model, validation study only	40.54	61.59	1.73 (0.34-8.88)	0.512	0.532
maximum likelihood estimate	6.80	32.5	1.10 (0.46-2.60)	0.834	0.045

[1] SD(Z) = 128.7, SD(X) = 13.54

[2] Likelihood ratio test

[3] Rosner B, Spiegelman D, Willett W. Correction of logistics regression relative risk estimates and confidence intervals for measurement error: the case of multiple covariates measured with error". Am J Epidemiol 1990; 132:732-745.

As expected, the logistic regression estimate over-estimates the prevalence ratio in analyses both corrected and uncorrected for exposure measurement error. The estimated log prevalence odds ratio ( ) for a one dose/week increment increases 7-10 fold after correction for measurement error, when using both the constant prevalence odds model with the Rosner et al. correction, and using the maximum likelihood measurement (ML) error model. With ML methods but not with the Rosner et al. correction procedure, the association remained statistically significant (p=0.045) after adjustment for measurement error. This is not surprising, as ML methods are maximally efficient assuming the model is correct.

Because they obviate the need to make distributional assumptions about the measurement error process, semi-parametric models are also being considered.

Generation of Fibrous Aerosols in Narrow Size Ranges

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Importance to Occupational Safety and Health

It has long been recognized that durable fibrous materials (asbestos and Man-Made Mineral Fibers (MMMF)) can become carcinogenic when

aerosolized. It has also been accepted that the physical properties of the fibers can be more important determinants of injury than its chemical ones. Due to the fibers' elongated geometries, the efficiencies of lung deposition and clearance for fibers can be significantly different from those of compact particles. Many studies have reported that shorter fibers are removed more effectively from lung than the longer ones. A review of published literature sources by HEI-AR (1991) demonstrates the critical importance of fiber dimensions and durability in tissues to the biological responses. However, there are still insufficient reliable experimental results to fully support the fiber size criteria and toxicity ranges. The difficulties of interpreting results from prior experimental animal and *in vitro* studies of responses to fiber exposures have been due, in part, to the wide-spread ranges of diameter and length of the administered fibers. The first aim of this study is to develop techniques for generating fibrous aerosols with various fibrous materials (asbestos and MMMF) in narrow size ranges for laboratory use. The generated fibers could be used directly in *in vitro, in vivo* instillation, or *in vivo* implantation studies, or could be resuspended (with some losses) for inhalation studies. With these high quality fibrous particles, the research on quantitative assessment of the inhalation hazard from aerosolized fibrous materials (asbestos and MMMF) can be conducted more definitively.

Objectives

Quantitative assessment of the inhalation hazard from aerosolized fibrous materials (asbestos and MMMF) requires geometrically defined fibers. The primary objective of the current proposal is to develop techniques for generating relatively monodisperse fibrous aerosols for laboratory use.

The specific aims of the project are:

1. To develop a system for generating relatively monodisperse fibrous aerosols for a variety of fiber types, both natural and man-made. It will consist of an inertial impactor, a virtual impactor and Nuclepore filters in cascade. The collected fibrous particles, which will have geometric standard deviations less than 1.50 for both diameter and length, will be used in future work to determine the inhalation hazard from fibers of various lengths, diameters, and fiber types.
2. Experimental and theoretical determination of the extent of influence of factors which affect collection characteristics of fibrous particles within sampling systems and lung airways.

Methodology

Polydisperse fibrous aerosols will first be generated by a fluidized bed fibrous generator (FBG) with number concentrations of 102-103/cc. The polydisperse fibrous aerosols will then be classified by an inertial impactor-virtual impactor system in diameter ranges of interest for subsequent biological effects testing, e.g., <0.15, 0.3-0.5, 2-3 μm. The fibrous aerosol in each diameter range then will be sorted by fiber length using Nuclepore filters under conditions where collection by interception is the dominant collection mechanism. Length cuts could be made at 2.5, 5, 10 and 20 μm. The system could be operated in cascade, collecting fractions with lengths <2.5, 2.5-5, 5-10, 10-20 and >20 μm. Our goal is to select fractions having narrow distributions of both fiber diameter and length, e.g., geometric standard deviation for both parameters will be less than 1.50.

Significant Findings

None to date.

Health Care Worker Compliance with Hepatitis B Vaccine

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Start & End Dates: *04/01/93 – 03/31/96*
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Importance to Occupational Safety and Health

The overall goal of this study is to evaluate the distribution and determinants of hepatitis B vaccine use and compliance in Iowa hospitals and among Iowa health care workers. This study is designed to identify institutional, occupational, and behavioral variables among health care workers that impact on their practice of effective preventive health measures, using compliance with the hepatitis B vaccine as the paradigm.

Objectives

We propose to test the following specific hypotheses:

1. that institutional levels of HBV vaccine compliance are directly related to the type of vaccine implementation program;
2. that high levels of institutional compliance with OSHA's Bloodborne Pathogens Rule will have indirect benefits on the frequency of sharps injuries, cutaneous exposures to blood, TB exposures, and PPD conversions
3. that the frequency of educational programs is unimportant in determining compliance in individual hospital workers;
4. that institutional factors including provision of the vaccine at the work site, increased access (availability), and documented informed refusal are more important than individual factors in determining individual compliance;
5. that compliance with universal precautions will predict compliance with HBV vaccination;
6. that social influence and facilitating conditions are extremely important in behavioral models of HCW vaccination behavior.

Methodology

In the first stage, a longitudinal survey of Iowa health care institutions will be performed over a two-year period to define the rates and distribution of hepatitis B vaccine compliance following implementation of a federal mandate for vaccination. Levels of institutional compliance with OSHA's Bloodborne Pathogens Rule will be categorized and their effect on vaccine compliance and occupational exposures measured. Vaccine compliance rates among health care workers in different job categories will be determined in institutional assessments at 12 and 24 months after the initial survey. In the second stage of the study, a stratified random sample of 15 health care workers in each of three occupational categories at 30 general hospitals will be studied to investigate attitudes about vaccination, the effectiveness of different types of vaccination programs, as well as the effect of OSHA's Bloodborne Pathogens Rule. Data from individual interviews will be used to evaluate the relative utility of two theoretical behavioral models in predicting health care worker vaccine compliance. Multi variate models will be developed to predict individual and institutional compliance. Additionally, the relative importance of institutional versus individual factors in determining individual hepatitis B vaccine compliance will be evaluated. In the third year of the study, these models will be validated prospectively in a second sample of health care workers and unstudied hospitals and used to identify an effective vaccine implementation program for hospitals and other health care facilities.

Significant Findings

Study 1: Hepatitis B Vaccination: Independent Predictors of Health Care Worker Compliance: We evaluated a 20% random sample of HCWs at risk for exposure to blood and body fluids at our tertiary care teaching center in Spring 1992; 908 of 1,018 (89%) questionnaires were returned. Only 54% had completed the HBV vaccine series, although 70% had received one or more doses. Significant univariate predictors of vaccination (1 or more doses) included: occupational category ($p<0.0001$), age ($p=0.0001$), previous influenza vaccination ($p=0.003$), and clinical setting ($p=0.0052$). The importance of reasons for vaccination (N= 13) or vaccine refusal (N=15) suggested by the literature and from our pilot testing of the questionnaire was assessed on a 7-point Likert scale and combined using factor analysis. The internal consistency (reliability) of each scale in this data (Cronbach's alpha statistic) in SPSS demonstrated an alpha of 0.72 for the reasons for refusal, and an alpha of 0.82 for the reasons for vaccination. The final logistic model for vaccine compliance included: occupational category ($p<0.0001$) and sharps injury ($p=0.0008$, Tables 3 and 4). The maximum likelihood ratio demonstrated the model fit the data well (Chi-Square=5.0, 5 DF, $p=0.416$). These data suggest that future vaccine implementation efforts must target specific occupational categories at risk, as well as HCWs during evaluation for sharps injury and possibly, cutaneous exposure. It is not certain that these determinants of individual HCW vaccination apply to HCWs in community hospitals and chronic care facilities. Final revision of the final structured interview form for the health care worker study is underway. Study 2: Hepatitis B Vaccination: Institutional Predictors: The Iowa Statewide Surveillance System (ISSS) is composed of representatives from all hospitals (N=128) and the largest chronic care facilities (N=13) in Iowa with trained infection control practitioners and ongoing surveillance for nosocomial infections. We developed a questionnaire to evaluate current HBV vaccine implementation programs in Iowa hospitals prior to OSHA's Bloodborne Pathogens Rule becoming law. The questionnaire was pilot tested, then administered to infection control practitioners (ICPs) at the 128 hospitals and 13 chronic care facilities in the ISSS. Two serial mailings were performed, with 133 of 141 (94%) returned. Telephone interviewing was performed to verify the data and complete missing items. Hospitals were stratified by their location in an urban versus rural county, based upon census data.

Counties were divided into urban/rural quartiles, based upon the proportion of the population of the county residing in a single incorporated place of more than 2,500 inhabitants. Mean rates of vaccination (three or more doses) in different occupational groups in urban versus rural counties ranged from 63% to 54% among housekeepers, 46% to 52% among physicians, and from 70% to 65% among laboratory workers. Data regarding rates of vaccination among physicians are limited in that most are not considered hospital employees and records were not available. Vaccine implementation programs also differ red considerably by size of the institution and whether it was located in an urban versus a rural county. Regression analysis to predict vaccination rates demonstrates that a variety of program characteristics are significantly associated with vaccination rates among workers. Data collection for the follow–up study of vaccine provision program characteristics and rates of vaccination among health care workers at 18 months after OSHA's guidelines becoming enforceable is currently underway.

Elevated Blood Leads in the Iowa Construction Industry

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Importance to Occupational Safety and Health

Sentinel data from case reports and surveillance systems strongly indicate that workers in selected construction trades are significantly exposed to lead, are inadequately monitored, and are sustaining serious illness from exposure. Although OSHA's new lead standard for the construction industry should help provide a framework for evaluation and control of lead exposures, there remains an acute need to determine the true scope of the problem and identify contributing risk factors. The results of this study will be useful for developing intervention strategies, and prioritizing prevention activities.

Objectives

The objectives of this project are to: characterize the prevalence of blood lead concentrations in selected high risk construction trades in the State of Iowa; identify and evaluate risk factors that may contribute to occupational exposure to lead in construction; evaluate the utility of using the Iowa Department of Public Health's (IDPH) Adult Blood Lead Surveillance Project for identification and mitigation of lead poisoning cases in construction; evaluate compliance with the new OSHA construction lead standard; collect, organize, and disseminate information concerning lead hazard and controls via the National Hazard Communication Resource Center (NHCRC) and presentations to construction workers; develop intervention strategies and future projects to quantitatively evaluate lead exposure in construction.

Methodology

This project involves a cooperative effort between the University of Iowa and the Eastern Iowa Construction Alliance, a labor management organization representing approximately 100 construction contractors and more than 3,400 union members. A sample of 500 workers will be randomly selected from the total population of all union members, using union records. 100 workers will be selected from each of the following high risk trade groups: painters, plumbers and pipe fitters, ironworkers, laborers, and electricians. Venous blood samples will be collected from each participant and analyzed for lead using atomic absorption spectroscopy. Information on demographics, symptoms, occupational history, work practices, personal protective equipment, training, other potential risk factors and confounders will be gathered using questionnaires at the same time that blood samples are collected. Awareness of, and compliance with OSHA's construction lead standard will also be ascertained. The primary objectives of data analysis will be to describe the distribution of blood lead concentrations, test the null hypothesis that there are no significant differences between the blood lead concentrations of workers in different trade groups, and evaluate the relationships between risk factors, symptoms, and blood lead concentrations. Results will also be used to evaluate the efficacy of the IDPH's Adult Blood Lead Surveillance Program, and the University of Iowa Hospital and Clinics' data base for identification and control of occupational exposure to lead in the Iowa construction industry. Upon completion of the prevalence study, and using the resources of the NHCRC, focus groups will be conducted with construction workers to present the findings and explore methods for reducing exposure.

Significant Findings

None to date.

An Exposure Matrix For Construction Painters

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Importance to Occupational Safety and Health

Construction painters are exposed to a wide variety of substances that may cause acute and chronic adverse health effects. Relatively little work has focused on this occupational group despite the extent of exposure, the large population of workers, and the potential for severe effects –neurotoxicity, increased accident rates, cancer, reproductive disorders, and respiratory disease. The investigation will provide much needed quantitative information on exposures in construction painting. By focusing on specific work tasks, a new methodology will be developed in which exposures can be accurately estimated on the basis of self reports of work activity. This exposure assessment technique will be valuable when dealing with workers who perform tasks at different jobsites or who perform a variety of activities. The new technique will enhance the capabilities of health scientists in the assessment of exposure of individuals that in the past have been difficult to characterize.

Objectives

The major hypothesis of the study is that by studying specific job tasks, a construction painter's overall occupational exposure can be estimated. In order to test this hypothesis, methods are under development to standardize the measurement of organic vapor exposures during specific construction painting tasks. Another important objective of the study is to determine the relationships between occupational exposures and variables that characterize the work environment. Through the analysis of data collected during this investigation a method will be developed that will allow the prediction of overall occupational exposures based on descriptions of work tasks and characteristics of the occupational environment.

Methodology

Measurements of exposures during specific work tasks will be evaluated for 200 construction painters in Colorado. The focus of the exposure assessments will be organic vapors. Collection and analytical techniques will vary depending on the expected contaminants in the work environment and the expected durations of exposure. Gas chromatography and IR spectrophotometry will be extensively used methods of analysis. Video taping of the work tasks will be undertaken to assist in the collection and interpretation of data.

A database of tasks and exposure levels will be developed for later use in the characterization of exposure on the basis of information from self–reported activities. Self–reported work activities will be obtained through the administration of a task history questionnaire. The statistical relationships between variables that characterize the work (tasks and environment) and exposure levels will be determined. Information obtained at the job sites will be used to develop and modify the task history questionnaire, and statistical analyses will be performed to assess its' utility in developing overall exposure profiles. A short questionnaire will be administered before and after each workshift in order to assess the relationship of painting exposures on the incidence of specific symptoms. The statistical associations between peak and time weighted average exposure levels and symptom scores will be determined.

Significant Findings

None to date.

TCD as a Screening Procedure for Exposures to Toxicants

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Importance to Occupational Safety and Health

Each year, thousands of new chemicals are developed and many eventually come into contact with people on the job or simply through everyday activities. Although every effort is made to ensure that each chemical is safe for human exposure, any new testing procedure that may potentially detect subtle changes occurring prior to observing clinical symptoms would certainly be worth further investigation. If subtle changes can be detected early enough, perhaps the chance of permanent damage occurring could be reduced or even eliminated completely.

Objectives

The purpose of this experiment was to use transcranial Doppler sonography (TCD) in the dog to noninvasively measure changes in cerebral blood flow (CBF) resulting from a low–level exposure to the commonly used pyrethroid insecticide deltamethrin. TCD has been well established as a noninvasive and cost effective means of measuring CBF in man. Although the use of TCD in animals has been limited, pilot work indicated that CBF can be measured in normal greyhound dogs. Further, it was shown that manipulations of CBF (using CO_2) can be detected using TCD. Deltamethrin has previously been shown to increase CBF in rats as determined by other techniques.

Methodology

In this experiment, deltamethrin was dissolved in glycerol–formal solvent and administered intravenously at dosage levels of 5% and 10% of the LD_{50} value to 12 adult dogs 48 hours apart. It was expected that vascular changes resulting from these low–level deltamethrin exposures would be subtle and occur over several minutes (rather than beat–to–beat changes). To test this hypothesis, mean blood flow velocity (MBFV) in the middle cerebral artery, mean arterial blood pressure (MAP) in the aorta, end tidal CO_2 (pCO_2), mean heart rate (MHR) and concentration of deltamethrin in the blood were measured during control, glycerol–formal and exposure (deltamethrin in glycerol–formal) periods according to a randomized block factorial design. In addition to the aforementioned parameters, systolic–to–diastolic ratio (SDR), Pourcelout pulsatility index (PPI), Gosling pulsatility index (GPI) and systolic upstroke (SU) were calculated using the blood flow velocity waveform.

Significant Findings

An analysis of variance was performed on each parameter to determine if there were significant differences among the three treatment groups. With respect to control levels, glycerol–formal alone did not exhibit significant effects on any of the physiological parameters measured. However, there was a significant decrease in SDR, PPI and GPI associated with the administration of glycerol–formal. This suggested that the shape of the blood flow velocity waveform changed in the presence of glycerol–formal without any corresponding changes in the measured physiological parameters. Following the administration of deltamethrin, there was a significant increase in MBFV lasting 10 minutes post exposure, a significant increase in MAP and decrease in MHR lasting 20 minutes post exposure and a significant increase in pCO_2 lasting 30 minutes post exposure. The increase in MBFV was expected and corroborates the increase in CBF previously observed in rats. These changes indicate that the deltamethrin was having systemic effects on the cardiovascular and cerebrovascular systems. Further, this data agrees with circulating deltamethrin concentrations in the blood which peaked approximately 5 minutes post exposure. SDR, PPI and GPI returned to control levels following the administration of deltamethrin. TCD seems to have significant potential as a screening methodology, however, to date, it has not been used with animals nor has it been applied in the field of toxicology. In this research, it has been shown that TCD is sensitive to alterations in CBF caused by deltamethrin in the greyhound dog.

Publications

Drues ME, Hopper DL, Lange DN: Transcranial Doppler Sonography: A New Noninvasive Method for Measuring Toxicant–Induced Alterations in Cerebral Blood Flow. Journal of Ultrasound in Medicine and Biology, 1992 (publication pending)

Drues ME, Hopper DL, Lange DN: A System for Detecting Chemically–induced Changes in Cerebral Blood Flow Using Transcranial Doppler Sinography in A Dog Model. Proc of the Fifth Annual IEEE Symposium on Computer–based Medical Systems. Duke University, Durham, North Carolina, pp. 477–485, June 14–17, 1992

Dose-Response Assessment Issues in Occupational Studies

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Program Area: *Other Occupational Needs*
Grant Number: *1 R03 OH02971-01A1*
Start & End Dates: *09/30/92 – 09/29/94*
Funding Level: *$0 ($19,363 Cum)*

Importance to Occupational Safety and Health

Dose–response assessment is used as a criterion in establishing causality on the basis of observational studies, and is used to improve understanding of biologic mechanisms. Additionally, it is used to set exposure standards in occupational and environmental settings. Biases in dose–response assessment can occur due to competing risks from morbidity and mortality that manifest as a healthy worker survivor effect. This project is examining the use of a job instability index as a surrogate for job– and dose–related morbidity. Results from this project may be used to increase the sensitivity of analyses of occupational studies that utilize quantitative exposure measures, and hence to improve the ability to set appropriate regulatory standards.

Objectives

The objective of this project is to determine ways to detect and quantify biases that may alter dose–response relationships in occupational studies.

Methodology

Exposure–related morbidity is being assessed using as a surrogate, gaps in employment. The association between exposure and this index of job instability is characterized using Cox hazard regression with time–dependent exposure variables (cumulative exposure, as well as current exposure), controlling for other variables such as age and date of hire. Relationships between gaps in employment and pre–retirement job leaving are also characterized by means of similar proportional hazards regression models, with gaps in employment representing an additional time–dependent variable. The association of this surrogate for exposure–related morbidity and respiratory cancer mortality is analyzed. Competing risks from other causes of death may also be related to exposure and will be analyzed as outcomes in their own right, using hazard regression models.

Significant Findings

Empirical findings indicate a strong association between gaps of 30 days or more and the following variables: age–at– hire; year–of–hire; cumulative exposure up to one year previously; current exposure in the preceding year. Younger age at hire, later year of hire, higher cumulative exposure, and lower current exposure were all associated with the risk of a 30–day gap. Three of these variables also show an interaction with time since hire. In particular, as time since hire increases, the positive association with cumulative exposure declines, the negative association with current exposure increases in absolute magnitude, and the positive association with year of hire increases.

Gaps in employment are positive predictors of early job– leaving, i.e., termination prior to retirement age. This association continues to hold after controlling for exposure and age and year of hire. Given the predictiveness of gaps in employment, it appears to be a useful index of job instability.

A Volatile Aerosol Sampler and Particle Size Analyzer

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Program Area: *Other Occupational Needs*
Grant Number: *5 R03 OH03039-02*
Start & End Dates: *09/30/92 – 09/29/94*
Funding Level: *$28,100 ($50,595 Cum)*

Importance to Occupational Safety and Health

Assessment of worker exposure to a volatile organic chemical (VOC) requires measuring the airborne concentration of the vapor phase and the coexisting particle phase separately, because the resulting inhalation dose can differ substantially. American Conference of Governmental Industrial Hygienists (ACGIH) has suggested establishing dual Threshold Limit Values (TLVs) for the two phases of a volatile substance. However, due to particle evaporation and vapor absorption by the particle surface in the sampling process, air samplers presently in use are not adequate for efficient separation of the VOC vapor and particles; and currently, there are no simple field sampling methods to measure the size distribution of particles that contain VOCs. The proposed VPS sampler and the MVPS particle size analyzing system will be appropriate for monitoring the airborne concentrations of VOCs in the industrial spray work environment, such as the reinforced plastic industry and the paint spray booth. They are relatively simple and inexpensive field sampling devices and will provide essential data for the assessment of worker exposure to the vapor and particle phases of a VOC and important reference data for establishing dual Threshold Limit Values (TLVs) for both phases. The same principle may also be applied for sampling and size classifying the particles that contain volatile, or semi-volatile components that are traditionally sampled with other sorbent collectors (silica gel, porous polymer, etc.).

Objectives

The first goal of this work is to develop a prototype Vapor/Particle Sampler (VPS) for rapid anisokinetic separation of the vapor phase and coexisting particle phase of an airborne VOC substance into gaseous and particulate fractions according to their differential inertia. Our second goal is to develop a prototype Multiple Vapor/Particle Sampler (MVPS) system, which not only can separate vapor and particles, but also can provide the size classification of the particles that contain VOCs. The aerodynamic cut-off sizes of the MVPS system will be designed to 1, 2, 4, 10 and 20 μm aerodynamic diameters, where, 4 and 10 μm are the ACGIH defined particle cut sizes for respirable and thoracic particulate mass fractions, respectively.

Methodology

The VPS sampler is designed for anisokinetic separation of the vapor molecules and particles into two identifiable fractions due to their differential inertia. The MVPS sampler system is designed to measure the particle size distribution of VOC containing particles by using a series of single-stage virtual impactors of designed cut-off size. Experimental studies are carried out to determine the optimum sampler geometric parameters, flow conditions and sampling time for efficient (>90%) separation of vapor and particles with reasonable sensitivity.

Laboratory-generated vapors and aerosols are used for sampler calibration and performance evaluation. A vibrating orifice aerosol generator is employed to produce monodisperse fluorescein-tagged oleic acid particles in the particle size range greater than 1 μm. Monodisperse submicron fluorescein particles are obtained from a system that includes a Collison nebulizer, an electrostatic classifier (DMA), and a condensation particle counter. The mass concentrations of fluorescein-tagged oleic acid particles or fluorescein particles are quantitatively analyzed by fluorometry. The sampling efficiencies will be measured at various inlet flow rates and various ratios of the dichotomous flow rates. The vapor collection efficiencies are tested in a chamber equipped with a vapor generating device and particle-free dilution air. Toluene, xylene and styrene are chosen as the test materials. The intersampler comparison tests are also carried out by comparing: (1) the VPS measurements of monodisperse particle concentration from the glassfiber filters; (2) the VPS measurements of airborne vapor concentration from charcoal sorbent tubes and 3M diffusion monitors; (3) the MVPS measurements of particle size distribution from a Climet Particle Size Analyzer and a multi-stage Mercer Cascade impactor.

Significant Findings

The preliminary design of the prototypes of VPS sampler and MVPS sampler system has been completed. A prototype VPS Sampler has been designed and fabricated. The sampler is designed to operate at a sample inlet flowrate 1.8 LPM, which can be conveniently and reliably provided by lightweight, commercial personal sampling pumps. The optimum sample geometrical parameters, such as nozzle diameter and length, distance of nozzle to filter, have been examined. The experimental tests and calibration of the VPS sampler have been carried out. The particle cut-off diameter (D_{50}) of the VPS sampler is 0.95 μm, which is determined from the particle collection efficiency as a function of particle aerodynamic diameter. Intersampler comparison results showed a good agreement between the mass concentration data of monodisperse particles measured by VPS sampler and the 37 mm Glassfiber filters (GF) with a correlation of (C_{VPS}/CGF) = 0.96

± 0.06 (95% confidence interval, n=13). An average wall loss of the VPS sampler is 2.2%.

The experimental tests and calibration of the MVPS system will be completed in the second year of the two year grant.

Training and Medical Surveillance Under the ETO Standard

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Program Area: *Other Occupational Needs*
Grant Number: *1 R03 OH03088-01*
Start & End Dates: *08/01/93 – 07/31/95*
Funding Level: *$17,281 ($17,281 Cum)*

Importance to Occupational Safety and Health

Broadly speaking, this study addresses the implementation of training and medical surveillance. Historically, training and medical surveillance have been emphasized and studied less than other preventive measures, such as engineering controls and exposure monitoring, which focus more directly on the source of exposure. Training and medical surveillance are generally assumed to occur and to have some preventive impact; however, systematic evaluation of these areas is only recently becoming recognized as a research need. Systematic study will help to develop untapped preventive potential of training and medical surveillance, fostering the development of a more integrated and balanced approach to hazard control at all levels.

The general aim of this study is to critically evaluate the implementation of the training and medical surveillance (MS) provisions of the Occupational Safety and Health Administration's (OSHA) 1984 Ethylene Oxide (EtO) Standard in the hospital setting. The broader goal of this research is to identify strengths and weaknesses of training and MS implementation in substance–specific OSHA standards in order to provide for more effective practice, enforcement strategies, and policy–making in these areas.

Objectives

The following three specific hypotheses, derived directly from the implementation strategies of exposure monitoring–driven substance–specific health standards will be tested: Hypothesis (1) Exceedance of trigger exposure levels is positively associated with implementation of EtO training, and Hypothesis (2) exceedance of trigger exposure levels is positively associated with implementation of EtO medical surveillance. Two EtO exposure levels are specified to trigger training and MS requirements: the Action Level of 0.5 ppm Time–weighted Average (TWA) and the Excursion Limit of 5 ppm TWA per 15 period. We are asking to what extent employers are in compliance with these requirements and to what extent exposure monitoring specifically guides employers in the implementation of EtO training and MS. Hypothesis (3): the implementation of training is positively associated with the implementation of medical surveillance. As stated in current OSHA policy, part of the intent of training is to make workers aware of their rights under a standard, which in turn is presumed to make workers more likely to exercise those rights. We will test for an association which would be consistent with such a causal relationship between training and MS.

Methodology

To achieve the specific aims, our approach integrates theory and principles from occupational health, health education, and the social sciences with survey research methodology. All Massachusetts hospitals were contacted by mail and surveyed for the use of EtO. To date, 93 have responded as EtO users, 63 as non–users. Only 4 of the 160 hospitals in the state have not responded. EtO users are then administered a 15 minute standardized telephone interview, followed by a standardized 1–2 hour face–to–face interview with the sterilization department supervisor. The telephone and face to face interviews are still in progress. Response rates to date are between 80 and 90% of EtO users. Brief questionnaires on health and safety support (professionals on staff, etc.) are also mailed to hospital health & safety departments, and brief questionnaires on the process and findings of EtO medical surveillance exams are mailed to providers wherever EtO medical surveillance has been provided.

Significant Findings

None to date.

Air Dispersion of Chemicals in Industrial Facilities

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Program Area: *Other Occupational Needs*
Grant Number: *1 R43 OH03009-01*
Start & End Dates: *09/30/92 – 07/31/93*
Funding Level: *$0 ($49,680 Cum)*

Importance to Occupational Safety and Health

Direct measurement is the traditional approach used to investigate exposure to airborne chemicals in the workplace. Modeling techniques can complement monitoring studies and provide a new tool for assessing air quality in workplaces. The ability to predict the behavior of chemicals may aid in the identification of causes of hazardous concentrations in indoor air and provide an opportunity to avoid such hazardous conditions prospectively. Modeling may also serve as a cost–effective screening tool that can be used in conjunction with monitoring to examine an environment more rigorously and to suggest optimal locations at which measurements should be taken.

Objectives

The overall goal of this work is to develop user–friendly software for modeling the concentrations of hazardous chemicals in indoor air. The aim of the Phase I study was to develop an approach to predict the dispersion of chemicals in indoor settings in which pollutants are not distributed uniformly. Subsequent research (if undertaken) will extend modeling capabilities to include fluid dynamic simulation and other predictive tools for assessing indoor air quality.

Methodology

Most models available for assessing indoor air quality are designed to simulate pollutant behavior in well–mixed regions throughout which contaminants are distributed uniformly. Such models are inappropriate, however, in industrial settings in which pollutants may be introduced or removed at numerous locations, thus leading to gradients in pollutant concentrations. The Phase I research study utilized an interactive software package called SIMULINK™ to develop a user–friendly modeling environment to simulate the behavior of pollutants in large, open indoor settings in which contaminant concentrations may vary greatly. A set of modeling elements were developed that can be used as building blocks to simulate pollutant dispersion. The physical processes considered include pollutant emission, transport, chemical reactions, local ventilation, and deposition to surfaces. Volume elements are used to represent subregions of the workplace that can reasonably be assumed to be well–mixed, and Exchange elements serve as linkages that specify pollutant transport between adjacent Volume elements. The modeling approach is demonstrated in the final Phase I report for a number of illustrative benchmark problems. In addition, two detailed examples illustrate practical applications of the modeling approach. In the first application, the simulation of ozone concentrations in a commercial setting suggests that both internal and external sources may contribute to exposure to ozone indoors, and that exposures may vary with significantly with proximity to sources. The second application was a retrospective study of toluene diisocyanate in a polyurethane manufacturing facility that was the focus of a detailed industrial hygiene survey. Using limited measurements of air flow velocities, the modeling simulation reproduced the pattern of toluene diisocyanate concentrations measured throughout the factory. In its current formulation, the modeling approach requires the specification of air flow data. Future research efforts (if undertaken) will investigate predictive tools for simulating air flow patterns in the absence of detailed empirical data.

Significant Findings

SIMULINK™, an interactive software package for modeling dynamic systems, has been used to develop a set of indoor air modeling elements. These elements can be used to simulate the time–dependent behavior of pollutants in indoor environments.

Micromachined System For Selective Measurement of VOCs

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Program Area: *Other Occupational Needs*
Grant Number: *1 R43 OH03102-01*
Start & End Dates: *09/15/93 – 08/14/94*
Funding Level: *$49,975 ($49,975 Cum)*

Importance to Occupational Safety and Health

Vapor–phase chemical detection is important in industrial hygiene and indoor air quality assurance. However, existing chemical–sensing technologies do not meet the needs in these areas adequately, particularly for portable air–quality instrumentation.

Sensors for personal chemical–exposure monitors must be reliable, have sufficient sensitivity to detect a fraction of the OSHA–dictated permissible exposure limit, and have high selectivity to the target chemical in the presence of interferents. They should also be small, inexpensive, fast–responding, and energy–efficient so that they can operate on batteries for extended periods. Existing sensor technologies do not meet these requirements, either because they are too expensive and complicated to use, or too limited in their capabilities. The sensing technology we propose is designed to overcome these limitations, so that it can be widely employed in occupational health and safety and in other applications.

Objectives

The goal of this research is to make a chemical measurement system for real–time detection of volatile organic compounds (VOCs) using a silicon micromachined system of components, such as ultrasonic flexural–plate–wave sensors. This system will be designed for use in personal chemical–exposure monitors. It will be small, inexpensive, robust, battery–operated, sensitive enough to detect VOCs at a fraction of the OSHA permissible exposure level, and selective enough to identify toxic chemicals in a realistic environment.

Methodology

Work in this phase focuses on three interrelated tasks: (1) design and fabrication of prototype chemical–identification chips that incorporate micromachined chemical–sensing components; (2) optimization of computer–based algorithms that control and coordinate the function of these components and analyze output data; (3) tests of the ability of the micromachined system to sense specific volatile organic compounds in the presence of interferants, including water vapor. The first–generation chip includes an ultrasonic flexural–plate–wave sensor and a preconcentrator with its associated heater.

Significant Findings

We have designed, built and tested a first–generation chemical–identification chip, associated drive circuitry and a data acquisition and control system. Electrical testing shows that the individual chip components function as designed: the preconcentrator temperature can be pulsed to 150 °C for over 1,000 cycles with no noticeable degradation or drift; the flexural–plate–wave sensors operate stably and respond to organic vapors; the computer–based control system allows us to coordinate the action of the micromachined components and the vapor–generation system, and to process, display and log data in real time.

Initial vapor–sensing tests show that attention must be paid to physical interaction between the system components. Changes are being made to the vapor generation system, and to the design of the chip in order to improve performance.

Personal Monitor For Toxic Vapors

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Program Area: *Other Occupational Needs*
Grant Number: *1 R43 OH03103-01*
Start & End Dates: *09/15/93 – 08/14/94*
Funding Level: *$49,616 ($49,616 Cum)*

Importance to Occupational Safety and Health

There is a need in the industrial workplace for small, sensitive, rugged, and easy–to–use personal monitors for toxic organic vapors. Many existing methods, e.g. electrochemical detectors, are not well suited for many toxic organic compounds and other methods such as dosimeter badges do not offer real–time response. The Surface Acoustic Wave (SAW) microsensor devices being developed in this

program are well suited for the real–time monitoring of high molecular weight, low volatility, toxic organics that are difficult to detect by other techniques.

Objectives

The objective of this program is to develop a miniature SAW vapor detection system with the size, sensitivity, reliability and power requirement appropriate for a pocket size Personal Monitor for Toxic Vapors. The aim of the Phase I effort is to develop a laboratory, or "breadboard" unit that demonstrates sensitivity to glutaraldehyde, a hazardous chemical used as a disinfectant for a number of medical applications, such as endoscope sterilization, and is very difficult to monitor by present detection technologies. In Phase II the detection capability of the Personal Monitor for Toxic Vapors will be extended to other hazardous vapors that are also difficult to detect by other means, such as the isocyanates. Also in Phase II, small, lightweight demonstration models of the Personal Monitor for Toxic Vapors will be designed, built, and evaluated.

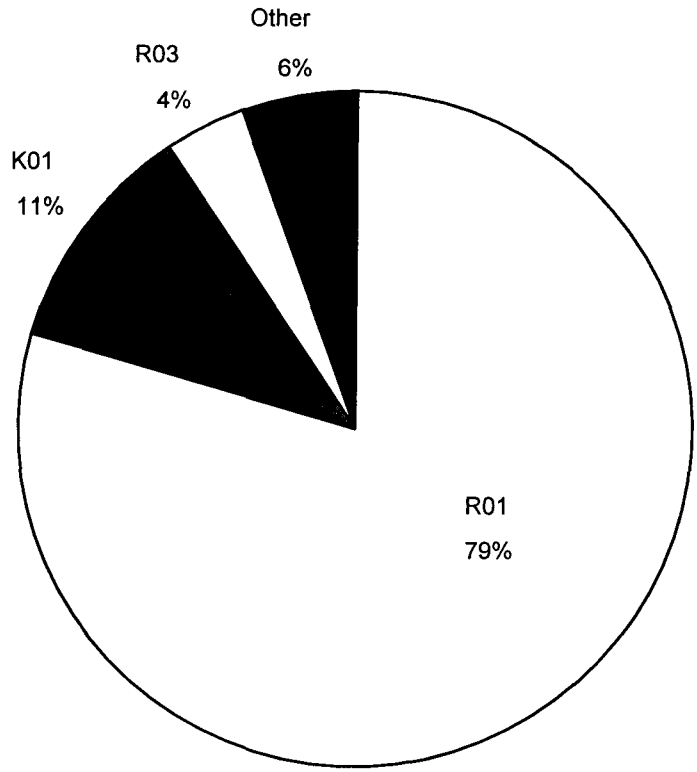
Methodology

The work being conducted in this phase I study is intended to show feasibility of the SAW microsensor approach. SAW vapor microsensors are surface mass sensitive micro–chip devices that can be made sensitive to organic vapors by the application of a suitable sorbent coating. Specific tasks in this program include development of a calibrated system to generate glutaraldehyde vapor, fabrication of a sensor electronic test system, coating of the SAW devices with a variety of sensitizing films, and evaluation of the sensor responses when challenged by known concentrations of glutaraldehyde vapor.

Significant Findings

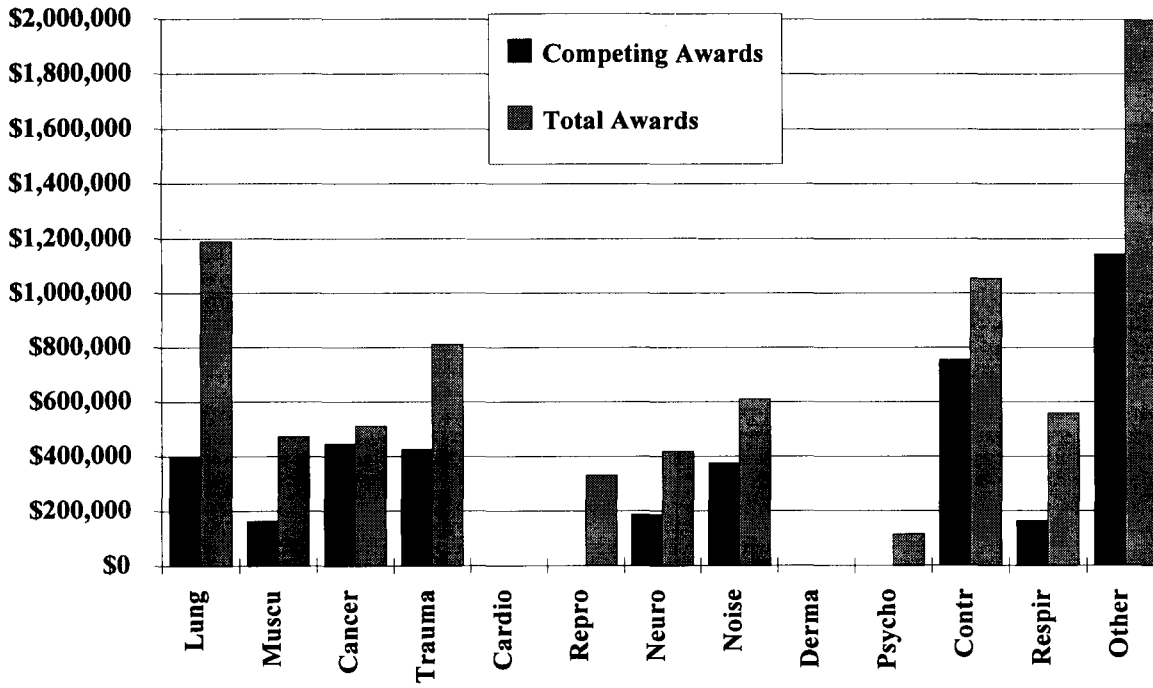
None to date.

FY93 Grant Awards by Activity
Percentage of Total Budget



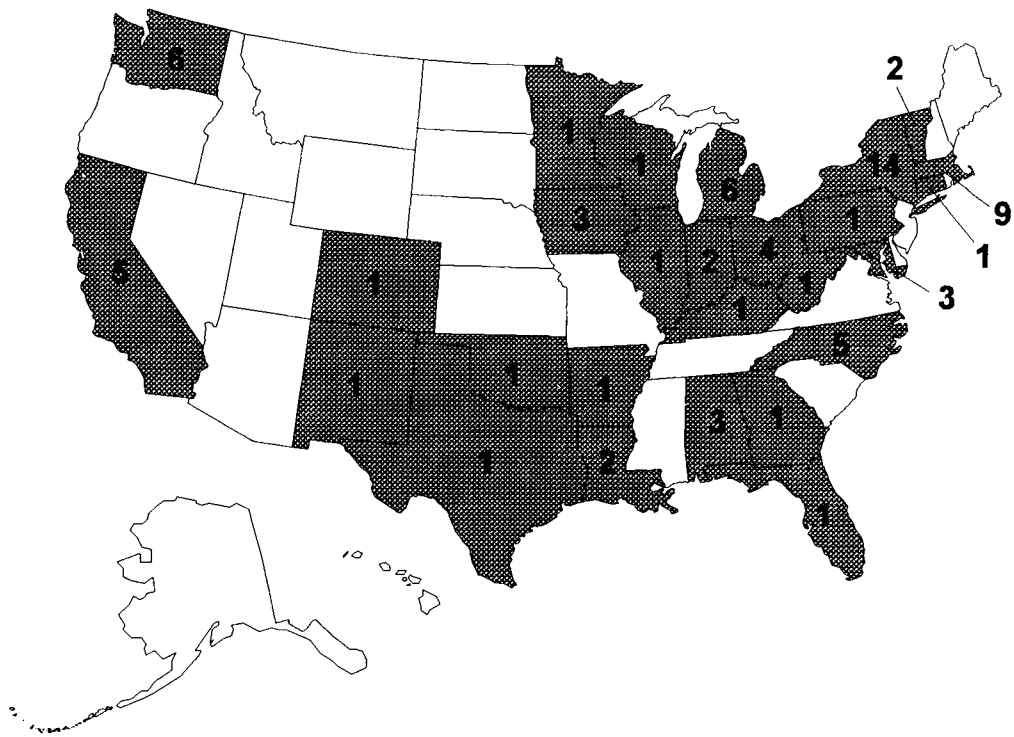
Activity	New Awards No.	New Awards Amount	Continuation Awards No.	Continuation Awards Amount	TOTAL Awards No.	TOTAL Awards Amount
R01	19	$3,089,086	25	$3,329,535	44	$6,418,621
K01	9	$476,088	8	$431,617	17	$907,705
R03	6	$182,956	6	$117,684	12	$300,640
Other	4	$313,274	1	$130,863	5	$444,137
Total	38	$4,061,404	40	$4,009,699	78	$8,071,103

FY93 Grant Awards by Program Area
Competing and Total Dollars



Program Area	Competing Awards Number	Competing Awards Amount	Total Awards Number	Total Awards Amount
Lung	5	$400,788	11	$1,189,373
Musculoskeletal	4	$162,694	8	$472,704
Cancer	3	$445,054	5	$511,526
Trauma	4	$426,049	8	$811,976
Cardiovascular	0	$0	0	$0
Reproductive	0	$0	4	$330,701
Neurotoxic	2	$187,158	4	$417,920
Noise	2	$376,376	3	$610,053
Dermatological	0	$0	0	$0
Psychological	0	$0	1	$114,399
Control Techniques	5	$754,973	9	$1,055,058
Respirator	1	$164,458	5	$558,257
Other	12	$1,143,854	20	$1,999,136
TOTAL	38	$4,061,404	78	$8,071,103

FY93 Grant Awards by State
78 Totaling $8,071,103



State	Amount	%	State	Amount	%
Alabama	$399,449	4.9	Michigan	$808,837	10.0
Arkansas	$34,640	0.4	Minnesota	$12,814	0.2
California	$437,264	5.4	North Carolina	$410,389	5.1
Colorado	$53,535	0.7	New Mexico	$179,833	2.2
Connecticut	$218,211	2.7	New York	$1,518,857	18.8
Florida	$53,832	0.7	Ohio	$446,695	5.5
Georgia	$136,688	1.7	Oklahoma	$267,940	3.3
Iowa	$158,956	2.0	Pennsylvania	$114,330	1.5
Illinois	$35,515	0.4	Texas	$76,357	1.0
Indiana	$296,809	3.7	Vermont	$370,691	4.6
Kentucky	$49,616	0.6	Washington	$369,980	4.6
Louisiana	$181,466	2.2	Wisconsin	$53,681	0.6
Massachusetts	$986,288	12.2	West Virginia	$125,972	1.6
Maryland	$272,458	3.4			

Grant Number	Principal Investigator	FY93 Funding	Page
	Research Project Grants (R01)		
5 R01 OH00823-12	Mohamed B. Abou-Donia, Ph.D.	$0	90
5 R01 OH00835-14	William J. Swartz, Ph.D.	$82,973	84
5 R01 OH01122-09S1	Charles W. Kauffman, Ph.D.	$0	68
5 R01 OH01152-12	Donald Henderson, Ph.D.	$233,677	100
5 R01 OH02067-09	G. Marie Swanson, Ph.D.	$0	52
5 R01 OH02128-08	William W. Clark, Ph.D.	$0	102
5 R01 OH02148-07	Stephen F. Cleary, Ph.D.	$0	131
5 R01 OH02149-06	Ghulam A.S. Ansari, Ph.D.	$0	133
5 R01 OH02221-05	Stephen M. Rappaport, Ph.D.	$0	136
5 R01 OH02277-03	David Warshawsky, Ph.D.	$0	11
2 R01 OH02317-09	Roger P. Hamernik, Ph.D.	$198,536	105
5 R01 OH02391-03	Nabih R. Asal, Ph.D.	$0	138
5 R01 OH02421-04	David C. Christiani, M.D.	$139,344	12
5 R01 OH02434-05	Mohamed M. Ayoub, Ph.D.	$76,357	36
5 R01 OH02571-06	Irvin Schonfeld, Ph.D.	$114,399	108
5 R01 OH02593-04	E. Neil Schachter, M.D.	$147,561	14
2 R01 OH02611-04	Susan T. Bagley, Ph.D.	$0	110
5 R01 OH02622-03	Regina M. Santella, Ph.D.	$0	139
2 R01 OH02647-03	George P. Hemstreet, Ph.D.	$267,940	54
5 R01 OH02663-03	Edward T. Zellers, Ph.D.	$0	141
5 R01 OH02664-02	Roy Rando, Sc.D.	$98,493	143
5 R01 OH02666-04	Steven P. Levine, Ph.D.	$211,324	144
5 R01 OH02683-02	William Daniell, M.D., M.P.H.	$166,820	93
5 R01 OH02710-02	Michael R. Flynn, Sc.D.	$0	112
5 R01 OH02719-03	Diana Echeverria, Ph.D.	$0	94
5 R01 OH02730-02	Genevieve M. Matanoski, M.D., Dr.P.H.	$0	55
5 R01 OH02740-02	Venkat Venkatasubramanian, Ph.D.	$82,901	112
5 R01 OH02741-03	Laura Punnett, Sc.D.	$48,493	70
1 R01 OH02743-01A2	Kweku K. Bentil, Ph.D.	$106,833	71
5 R01 OH02758-02	Scott S. Campbell, Ph.D.	$142,120	146
5 R01 OH02761-02	Thomas G. Robins, M.D., M.P.H.	$0	17
5 R01 OH02767-03	Roberta F. White, Ph.D.	$176,762	96
5 R01 OH02772-04	Juraj J. Ferin, M.D.	$144,299	18
5 R01 OH02792-03	Roger W. Giese, Ph.D.	$136,446	147
5 R01 OH02794-02	Amit Bhattacharya, Ph.D.	$0	72
5 R01 OH02804-03	Richard A. Wadden, Ph.D.	$35,515	114
5 R01 OH02820-02	David Kriebel, Sc.D.	$0	56
5 R01 OH02858-03	Michael R. Flynn, Sc.D.	$59,540	115
5 R01 OH02872-03	Jess F. Kraus, Ph.D.	$193,325	73
5 R01 OH02885-03	Maureen C. Hatch, Ph.D.	$207,513	85
5 R01 OH02914-02	H. Kenneth Dillon, Ph.D.	$115,087	19
5 R01 OH02918-02	William T. Stauber, Ph.D.	$125,972	37
5 R01 OH02922-02	Yung-Sung Cheng, Ph.D.	$179,833	124
1 R01 OH02941-01	Alfred Franzblau, M.D.	$0	39
1 R01 OH02945-01	Om P. Gandhi, Sc.D.	$0	148
5 R01 OH02948-02	Klaus Willeke, Ph.D.	$147,152	125
5 R01 OH02951-02	Shane Que Hee, Ph.D.	$122,129	115
1 R01 OH02953-01A1	Ellen A. Eisen, Sc.D.	$123,282	57

Grant Number	Principal Investigator	FY93 Funding	Page
5 R01 OH02967-02	Bernard J. Martin, Ph.D.	$90,109	74
5 R01 OH02987-02	William S. Beckett, M.D.	$218,211	21
1 R01 OH03015-01A1	Phillip A. Bishop, Ed.D.	$153,499	116
1 R01 OH03021-01A1	Tomasz R. Letowski, H.D., Ph.D.	$114,330	117
1 R01 OH03024-01	Alfred Franzblau, M.D.	$176,191	150
1 R01 OH03033-01	Edward T. Zellers, Ph.D.	$116,453	118
1 R01 OH03044-01A1	Terry Gordon, Ph.D.	$97,953	22
1 R01 OH03052-01	Kyle D. Squires, Ph.D.	$152,013	119
1 R01 OH03056-01A1	Venkat Venkatasubramanian, Ph.D.	$213,908	151
1 R18 OH03073-01	Michael J. Symons, Ph.D.	$68,139	153
1 R01 OH03078-01	Richard E. Letz, Ph.D.	$136,688	97
1 R01 OH03079-01	Amit Bhattacharya, Ph.D.	$233,071	76
1 R01 OH03134-01	Michael G. Yost, Ph.D.	$119,762	154
1 R01 OH03136-01	Sally L. Lusk, Ph.D.	$177,840	107
1 R01 OH03157-01	Dryver R. Huston, Ph.D.	$218,678	120
1 R01 OH03168-01	John M. Dement, Ph.D.	$177,290	22
1 R01 OH03177-01	Lewis D. Pepper, M.D.	$236,680	155
	Career Development Grants (K01)		
5 K01 OH00076-03	Paul W. Brandt-Rauf, Sc.D., M.D.	$0	58
5 K01 OH00077-03	Edward T. Zellers, Ph.D.	$0	157
5 K01 OH00078-03	Lorraine M. Conroy, Sc.D.	$0	121
5 K01 OH00079-03	Paul D. Blanc, M.D.	$0	24
5 K01 OH00081-03	Gerald N. Levy, Ph.D.	$0	61
5 K01 OH00085-03	Riedar K. Oestenstad, Ph.D.	$0	126
5 K01 OH00087-03	Patrick N. Breysse, Ph.D.	$54,000	127
5 K01 OH00090-03	David G. Wilder, Ph.D.	$0	40
5 K01 OH00093-03	David A. Schwartz, M.D., M.P.H.	$0	26
5 K01 OH00098-03	Fredric E. Gerr, M.D.	$0	41
5 K01 OH00103-03	Lori A. Todd, Ph.D.	$53,936	158
5 K01 OH00106-04	Donna Spiegelman, Sc.D.	$54,000	159
5 K01 OH00107-03	Robert G. Radwin, Ph.D.	$53,681	42
5 K01 OH00108-02	Michael J. Kosnett, M.D.	$0	82
5 K01 OH00110-03	Karl T. Kelsey, M.D.	$54,000	62
5 K01 OH00115-02	Fabian C. Hadipriono, Dr.Eng.	$54,000	77
5 K01 OH00121-02	David M. Rempel, M.D.	$54,000	44
5 K01 OH00123-02	Rob McConnell, M.D.	$54,000	98
1 K01 OH00125-01A1	Lora E. Fleming, M.D.	$53,832	64
1 K01 OH00129-01A1	Ching-Ping Fang, Ph.D.	$53,811	161
1 K01 OH00131-01	Bradley N. Doebbeling, M.D.	$50,956	162
1 K01 OH00132-01	Jacqueline Agnew, Ph.D.	$54,000	45
1 K01 OH00133-01	Matthew C. Keifer, M.D.	$50,470	99
1 K01 OH00134-01	William D. Clapp, M.D.	$54,000	31
1 K01 OH00135-01	Gary A. Mirka, Ph.D.	$51,484	46
1 K01 OH00137-01	Stephen J. Reynolds, Ph.D.	$54,000	164
1 K01 OH00138-01	Philip L. Bigelow, Ph.D.	$53,535	165

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	Small Grants (R03)		
5 R03 OH02765-02	Hal Morgenstern, Ph.D.	$0	47
5 R03 OH02880-02	Suresh P. Krishnan	$0	65
5 R03 OH02931-02	David J. Brenner, Ph.D.	$24,083	31
5 R03 OH02932-02	Michael E. Drues	$0	166
5 R03 OH02938-02	Lisa M. Brosseau, Sc.D.	$13,096	128
5 R03 OH02966-02	Harvey Checkoway, Ph.D.	$22,380	87
1 R03 OH02971-01A1	Irva Hertz-Picciotto, Ph.D.	$0	167
5 R03 OH02972-02	Changhwa Jacob Cheu	$12,472	66
5 R03 OH03000-02	Marc B. Schenker, M.D.	$17,835	88
5 R03 OH03039-02	Judy Q. Xiong, Ph.D.	$28,100	167
1 R03 OH03061-01	Randal J. Keller, Ph.D.	$34,640	33
1 R03 OH03064-01	Mitchell D. Cohen, Ph.D.	$36,905	34
1 R03 OH03087-01	Ali Sheikhzadeh	$35,900	49
1 R03 OH03088-01	Anthony D. Lamontagne	$17,281	169
1 R03 OH03091-01	Bradley Evanoff, M.D.	$21,310	49
1 R03 OH03154-01	John G. Everett, Ph.D.	$36,920	79
	Small Business Grants (R43, R44)		
1 R43 OH02907-01	Beth Ann Marcus, Ph.D.	$0	50
1 R43 OH03009-01	Stephen G. Zemba, Ph.D.	$0	170
1 R43 OH03010-01	Peter J. Kajenski, Ph.D.	$0	122
1 R43 OH03018-01	Christopher C. Johnson	$0	123
1 R43 OH03099-01	Bob E. Hayes, Ph.D.	$49,225	80
1 R43 OH03102-01	Stuart W. Wenzel	$49,975	171
1 R43 OH03103-01	N. L. Jarvis, Ph.D.	$49,616	171
2 R44 OH03011-02	Clinton E. Brown	$164,458	129

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	Research Project Grants (R01)		
Abou-Donia, Mohamed B., Ph.D.	Neurotoxic Disorders	5 R01 OH00823-12	90
Ansari, Ghulam A.S., Ph.D.	Other Occupational Needs	5 R01 OH02149-06	133
Asal, Nabih R., Ph.D.	Other Occupational Needs	5 R01 OH02391-03	138
Ayoub, Mohamed M., Ph.D.	Musculoskeletal Injuries	5 R01 OH02434-05	36
Bagley, Susan T., Ph.D.	Control Techniques	2 R01 OH02611-04	110
Beckett, William S., M.D.	Occupational Lung Diseases	5 R01 OH02987-02	21
Bentil, Kweku K., Ph.D.	Traumatic Injuries	1 R01 OH02743-01A2	71
Bhattacharya, Amit, Ph.D.	Traumatic Injuries	1 R01 OH03079-01	76
Bhattacharya, Amit, Ph.D.	Traumatic Injuries	5 R01 OH02794-02	72
Bishop, Phillip A., Ed.D.	Other Occupational Needs	1 R01 OH03015-01A1	116
Campbell, Scott S., Ph.D.	Other Occupational Needs	5 R01 OH02758-02	146
Cheng, Yung-Sung, Ph.D.	Respirator Research	5 R01 OH02922-02	124
Christiani, David C., M.D.	Occupational Lung Diseases	5 R01 OH02421-04	12
Clark, William W., Ph.D.	Noise-Induced Hearing Loss	5 R01 OH02128-08	102
Cleary, Stephen F., Ph.D.	Other Occupational Needs	5 R01 OH02148-07	131
Daniell, William, M.D., M.P.H.	Neurotoxic Disorders	5 R01 OH02683-02	93
Dement, John M., Ph.D.	Occupational Lung Disease	1 R01 OH03168-01	22
Dillon, H. Kenneth, Ph.D.	Occupational Lung Diseases	5 R01 OH02914-02	19
Echeverria, Diana, Ph.D.	Neurotoxic Disorders	5 R01 OH02719-03	94
Eisen, Ellen A., Sc.D.	Occupational Cancers	1 R01 OH02953-01A1	57
Ferin, Juraj J., M.D.	Occupational Lung Diseases	5 R01 OH02772-04	18
Flynn, Michael R., Sc.D.	Control Techniques	5 R01 OH02710-02	112
Flynn, Michael R., Sc.D.	Control Techniques	5 R01 OH02858-03	115
Franzblau, Alfred, M.D.	Musculoskeletal Injuries	1 R01 OH02941-01	39
Franzblau, Alfred, M.D.	Other Occupational Needs	1 R01 OH03024-01	150
Gandhi, Om P., Sc.D.	Other Occupational Needs	1 R01 OH02945-01	148
Giese, Roger W., Ph.D.	Other Occupational Needs	5 R01 OH02792-03	147
Gordon, Terry, Ph.D.	Occupational Lung Diseases	1 R01 OH03044-01A1	22
Hamernik, Roger P., Ph.D.	Noise-Induced Hearing Loss	2 R01 OH02317-09	105
Hatch, Maureen C., Ph.D.	Disorders of Reproduction	5 R01 OH02885-03	85
Hemstreet, George P., Ph.D.	Occupational Cancers	2 R01 OH02647-03	54
Henderson, Donald, Ph.D.	Noise-Induced Hearing Loss	5 R01 OH01152-12	100
Huston, Dryver R., Ph.D.	Control Techniques	1 R01 OH03157-01	120
Kauffman, Charles W., Ph.D.	Traumatic Injuries	5 R01 OH01122-09S1	68
Kraus, Jess F., Ph.D.	Traumatic Injuries	5 R01 OH02872-03	73
Kriebel, David, Sc.D.	Occupational Cancers	5 R01 OH02820-02	56
Letowski, Tomasz R., H.D., Ph.D.	Control Techniques	1 R01 OH03021-01A1	117
Letz, Richard E., Ph.D.	Neurotoxic Disorders	1 R01 OH03078-01	97
Levine, Steven P., Ph.D.	Other Occupational Needs	5 R01 OH02666-04	144
Lusk, Sally L., Ph.D.	Noise-Induced Hearing Loss	1 R01 OH03136-01	107
Martin, Bernard J., Ph.D.	Traumatic Injuries	5 R01 OH02967-02	74
Matanoski, Genevieve M., M.D., Dr.P.H.	Occupational Cancers	5 R01 OH02730-02	55
Pepper, Lewis D., M.D.	Other Occupational Needs	1 R01 OH03177-01	155
Punnett, Laura, Sc.D.	Traumatic Injuries	5 R01 OH02741-03	70
Que Hee, Shane, Ph.D.	Other Occupational Needs	5 R01 OH02951-02	115
Rando, Roy, Sc.D.	Other Occupational Needs	5 R01 OH02664-02	143
Rappaport, Stephen M., Ph.D.	Other Occupational Needs	5 R01 OH02221-05	136
Robins, Thomas G., M.D., M.P.H.	Occupational Lung Diseases	5 R01 OH02761-02	17
Santella, Regina M., Ph.D.	Dermatological Conditions	5 R01 OH02622-03	139

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Schachter, E. Neil, M.D.	Occupational Lung Diseases	5 R01 OH02593–04	14
Schonfeld, Irvin, Ph.D.	Psychological Disorders	5 R01 OH02571–06	108
Squires, Kyle D., Ph.D.	Control Techniques	1 R01 OH03052–01	119
Stauber, William T., Ph.D.	Musculoskeletal Injures	5 R01 OH02918–02	37
Swanson, G. Marie, Ph.D.	Occupational Cancers	5 R01 OH02067–09	52
Swartz, William J., Ph.D.	Disorders of Reproduction	5 R01 OH00835–14	84
Symons, Michael J., Ph.D.	Other Occupational Needs	1 R18 OH03073–01	153
Venkatasubramanian, Venkat, Ph.D.	Control Techniques	5 R01 OH02740–02	112
Venkatasubramanian, Venkat, Ph.D.	Other Occupational Needs	1 R01 OH03056–01A1	151
Wadden, Richard A., Ph.D.	Control Techniques	5 R01 OH02804–03	114
Warshawsky, David, Ph.D.	Occupational Lung Diseases	5 R01 OH02277–03	11
White, Roberta F., Ph.D.	Neurotoxic Disorders	5 R01 OH02767–03	96
Willeke, Klaus, Ph.D.	Respirator Research	5 R01 OH02948–02	125
Yost, Michael G., Ph.D.	Other Occupational Needs	1 R01 OH03134–01	154
Zellers, Edward T., Ph.D.	Other Occupational Needs	5 R01 OH02663–03	141
Zellers, Edward T., Ph.D.	Control Techniques	1 R01 OH03033–01	118
	Career Development Grants (K01)		
Agnew, Jacqueline, Ph.D.	Musculoskeletal Injuries	1 K01 OH00132–01	45
Bigelow, Philip L., Ph.D.	Other Occupational Needs	1 K01 OH00138–01	165
Blanc, Paul D., M.D.	Occupational Lung Diseases	5 K01 OH00079–03	24
Brandt–Rauf, Paul W., Sc.D., M.D.	Occupational Cancers	5 K01 OH00076–03	58
Breysse, Patrick N., Ph.D.	Respirator Research	5 K01 OH00087–03	127
Clapp, William D., M.D.	Occupational Lung Diseases	1 K01 OH00134–01	31
Conroy, Lorraine M., Sc.D.	Control Techniques	5 K01 OH00078–03	121
Doebbeling, Bradley N., M.D.	Other Occupational Needs	1 K01 OH00131–01	162
Fang, Ching–Ping, Ph.D.	Other Occupational Needs	1 K01 OH00129–01A1	161
Fleming, Lora E., M.D.	Occupational Cancers	1 K01 OH00125–01A1	64
Gerr, Fredric E., M.D.	Musculoskeletal Injuries	5 K01 OH00098–03	41
Hadipriono, Fabian C., Dr.Eng.	Traumatic Injuries	5 K01 OH00115–02	77
Keifer, Matthew C., M.D.	Neurotoxic Disorders	1 K01 OH00133–01	99
Kelsey, Karl T., M.D.	Occupational Cancers	5 K01 OH00110–03	62
Kosnett, Michael J., M.D.	Cardiovascular Diseases	5 K01 OH00108–02	82
Levy, Gerald N., Ph.D.	Occupational Cancers	5 K01 OH00081–03	61
McConnell, Rob, M.D.	Neurotoxic Disorders	5 K01 OH00123–02	98
Mirka, Gary A., Ph.D.	Musculoskeletal Injuries	1 K01 OH00135–01	46
Oestenstad, Riedar K., Ph.D.	Respirator Research	5 K01 OH00085–03	126
Radwin, Robert G., Ph.D.	Musculoskeletal Injuries	5 K01 OH00107–03	42
Rempel, David M., M.D.	Musculoskeletal Injuries	5 K01 OH00121–02	44
Reynolds, Stephen J., Ph.D.	Other Occupational Needs	1 K01 OH00137–01	164
Schwartz, David A., M.D., M.P.H.	Occupational Lung Diseases	5 K01 OH00093–03	26
Spiegelman, Donna, Sc.D.	Other Occupational Needs	5 K01 OH00106–04	159
Todd, Lori A., Ph.D.	Other Occupational Needs	5 K01 OH00103–03	158
Wilder, David G., Ph.D.	Musculoskeletal Injuries	5 K01 OH00090–03	40
Zellers, Edward T., Ph.D.	Other Occupational Needs	5 K01 OH00077–03	157
	Small Grants (R03)		
Brenner, David J., Ph.D.	Occupational Lung Diseases	5 R03 OH02931–02	31
Brosseau, Lisa M., Sc.D.	Respirator Research	5 R03 OH02938–02	128

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Checkoway, Harvey, Ph.D.	Disorders of Reproduction	5 R03 OH02966-02	87
Cheu, Changhwa Jacob	Occupational Cancers	5 R03 OH02972-02	66
Cohen, Mitchell D., Ph.D.	Occupational Lung Diseases	1 R03 OH03064-01	34
Drues, Michael E.	Other Occupational Needs	5 R03 OH02932-02	166
Evanoff, Bradley, M.D.	Musculoskeletal Injuries	1 R03 OH03091-01	49
Everett, John G., Ph.D.	Traumatic Injuries	1 R03 OH03154-01	79
Hertz-Picciotto, Irva, Ph.D.	Other Occupational Needs	1 R03 OH02971-01A1	167
Keller, Randal J., Ph.D.	Occupational Lung Diseases	1 R03 OH03061-01	33
Krishnan, Suresh P.	Occupational Cancers	5 R03 OH02880-02	65
Lamontagne, Anthony D.	Other Occupational Needs	1 R03 OH03088-01	169
Morgenstern, Hal, Ph.D.	Musculoskeletal Injuries	5 R03 OH02765-02	47
Schenker, Marc B., M.D.	Disorders of Reproduction	5 R03 OH03000-02	88
Sheikhzadeh, Ali	Musculoskeletal Injuries	1 R03 OH03087-01	49
Xiong, Judy Q., Ph.D.	Other Occupational Needs	5 R03 OH03039-02	167
	Small Business Grants (R43, R44)		
Brown, Clinton E.	Respirator Research	2 R44 OH03011-02	129
Hayes, Bob E., Ph.D.	Traumatic Injuries	1 R43 OH03099-01	80
Jarvis, N. L., Ph.D.	Other Occupational Needs	1 R43 OH03103-01	171
Johnson, Christopher C.	Control Techniques	1 R43 OH03018-01	123
Kajenski, Peter J., Ph.D.	Control Techniques	1 R43 OH03010-01	122
Marcus, Beth Ann, Ph.D.	Musculoskeletal Injuries	1 R43 OH02907-01	50
Wenzel, Stuart W.	Other Occupational Needs	1 R43 OH03102-01	171
Zemba, Stephen G., Ph.D.	Other Occupational Needs	1 R43 OH03009-01	170

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Battelle Human Affairs Research Center	Diana Echeverria, Ph.D.	94
Boston University	Lewis D. Pepper, M.D.	155
Boston University	Roberta F. White, Ph.D.	96
California, University of	Jess F. Kraus, Ph.D.	73
California, University of	Shane Que Hee, Ph.D.	115
Central Institute for the Deaf	William W. Clark, Ph.D.	102
Cincinnati, University of	Amit Bhattacharya, Ph.D.	76
Cincinnati, University of	Klaus Willeke, Ph.D.	125
Cincinnati, University of	Amit Bhattacharya, Ph.D.	72
Cincinnati, University of	David Warshawsky, Ph.D.	11
City College of CUNY	Irvin Schonfeld, Ph.D.	108
Columbia University	Maureen C. Hatch, Ph.D.	85
Columbia University	Regina M. Santella, Ph.D.	139
Duke University	Mohamed B. Abou-Donia, Ph.D.	90
Duke University	John M. Dement, Ph.D.	22
Emory University	Richard E. Letz, Ph.D.	97
Harvard University	David C. Christiani, M.D.	12
Illinois, University of	Richard A. Wadden, Ph.D.	114
Johns Hopkins University	Genevieve M. Matanoski, M.D., Dr.P.H.	55
Louisiana State University	William J. Swartz, Ph.D.	84
Lovelace Biomedical & Environmental Res Institute	Yung-Sung Cheng, Ph.D.	124
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Lowell, University of	Laura Punnett, Sc.D.	70
Massachusetts, University of	Ellen A. Eisen, Sc.D.	57
Michigan State University	G. Marie Swanson, Ph.D.	52
Michigan Technological University	Susan T. Bagley, Ph.D.	110
Michigan, University of	Bernard J. Martin, Ph.D.	74
Michigan, University of	Charles W. Kauffman, Ph.D.	68
Michigan, University of	Alfred Franzblau, M.D.	39
Michigan, University of	Edward T. Zellers, Ph.D.	141
Michigan, University of	Sally L. Lusk, Ph.D.	107
Michigan, University of	Steven P. Levine, Ph.D.	144
Michigan, University of	Edward T. Zellers, Ph.D.	118
Michigan, University of	Alfred Franzblau, M.D.	150
Michigan, University of	Thomas G. Robins, M.D., M.P.H.	17
Mount Sinai	E. Neil Schachter, M.D.	14
New York Hospital - Cornell Medical Center	Scott S. Campbell, Ph.D.	146
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North Carolina, University of	Michael J. Symons, Ph.D.	153
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Northeastern University	Roger W. Giese, Ph.D.	147
Oklahoma, University of	Nabih R. Asal, Ph.D.	138
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State University of New York	Donald Henderson, Ph.D.	100
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West Virginia University	William T. Stauber, Ph.D.	37
Yale University	William S. Beckett, M.D.	21
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Alabama, University of	Riedar K. Oestenstad, Ph.D.	126
California, University of	Paul D. Blanc, M.D.	24
California, University of	David M. Rempel, M.D.	44
California, University of	Michael J. Kosnett, M.D.	82
Colorado State University	Philip L. Bigelow, Ph.D.	165
Columbia University	Paul W. Brandt-Rauf, Sc.D., M.D.	58
Emory University	Fredric E. Gerr, M.D.	41
Harvard University	Donna Spiegelman, Sc.D.	159
Harvard University	Karl T. Kelsey, M.D.	62
Illinois, University of	Lorraine M. Conroy, Sc.D.	121
Iowa, University of	Bradley N. Doebbeling, M.D.	162
Iowa, University of	William D. Clapp, M.D.	31
Iowa, University of	Stephen J. Reynolds, Ph.D.	164
Iowa, University of	David A. Schwartz, M.D., M.P.H.	26
Johns Hopkins University	Jacqueline Agnew, Ph.D.	45
Johns Hopkins University	Patrick N. Breysse, Ph.D.	127
Miami, University of	Lora E. Fleming, M.D.	64
Michigan, University of	Gerald N. Levy, Ph.D.	61
Michigan, University of	Edward T. Zellers, Ph.D.	157
Mount Sinai	Rob McConnell, M.D.	98
New York University	Ching-Ping Fang, Ph.D.	161
North Carolina State University	Gary A. Mirka, Ph.D.	46
North Carolina, University of	Lori A. Todd, Ph.D.	158
Ohio State University	Fabian C. Hadipriono, Dr.Eng.	77
Vermont, University of	David G. Wilder, Ph.D.	40
Washington, University of	Matthew C. Keifer, M.D.	99
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Cincinnati, University of	Changhwa Jacob Cheu	66
Cincinnati, University of	Suresh P. Krishnan	65
Columbia University	David J. Brenner, Ph.D.	31
Harvard School of Public Health	Anthony D. Lamontagne	169
Hospital For Joint Diseases	Ali Sheikhzadeh	49
Iowa State University	Michael E. Drues	166
Michigan, University of	John G. Everett, Ph.D.	79
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New York University	Judy Q. Xiong, Ph.D.	167
New York University	Mitchell D. Cohen, Ph.D.	34
North Carolina, University of	Irva Hertz-Picciotto, Ph.D.	167
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EXOS, Inc.	Beth Ann Marcus, Ph.D.	50
Medical Consultants Northwest, Inc.	Bob E. Hayes, Ph.D.	80
Microsensor Systems, Inc.	N. L. Jarvis, Ph.D.	171
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