

NIOSH

Research and Demonstration Grants

Annual Report Fiscal Year 1992



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

NIOSH

RESEARCH AND DEMONSTRATION GRANTS

FISCAL YEAR 1992



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

May 1993

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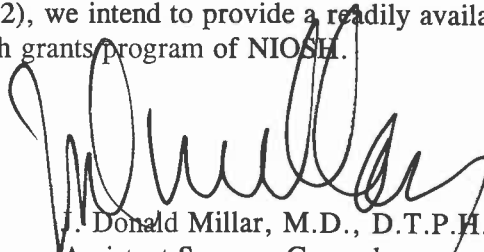
FOREWORD

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 develop recommendations for protecting workers of the United States against diseases and injuries related to risks on the job. In carrying out this mission, NIOSH plans, directs, and coordinates a national program of research, training, and related activities. To complement a substantial program of intramural research, NIOSH supports outstanding extramural research as a major component of its scientific endeavors.

Since 1984, the investment by NIOSH in both intramural and extramural research has focussed on "The Ten Leading Work-Related Diseases and Injuries." These are listed in Section H. ("Funding Priorities") in the program announcement included in this report (pages 4-10). In addition to the leading occupational diseases and injuries, we also emphasize research on engineering control methods and respiratory protection because of the crucial importance of these two areas to prevention.

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

We publish this report to stimulate submission of proposals for research of high quality on significant problems of occupational safety and health. We invite the interest of investigators in the biomedical sciences, engineering, and related disciplines. By including descriptions of all active grants during fiscal year 1992 (October 1, 1991 to September 30, 1992), we intend to provide a readily available source of information on the status and scope of the research grants program of NIOSH.



J. Donald Millar, M.D., D.T.P.H. (Lond.)
Assistant Surgeon General
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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 10,000 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?

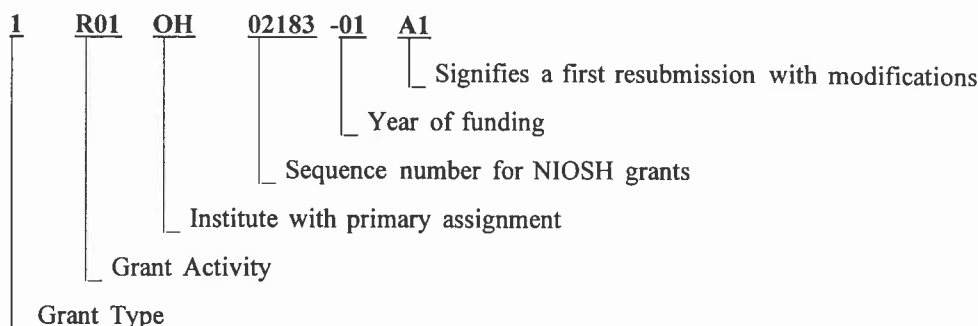
Contact NIOSH at the following address and telephone number:

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

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.

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

Of the total fiscal year 1993 budget of \$7,739,847, about \$4,480,000 is for non-competing continuation awards, and \$3,259,847 is for other new and competing renewal awards. The estimated breakdown for the new and competing renewal awards is as follows: R01 and R18 grants - 16 awards for \$2,414,847 (total costs of these awards range from \$50,000 to \$250,000 with the average award being about \$145,000); K01 grants - 8 awards for \$432,000; and R03 grants - 11 awards for \$413,000.

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 for setting priority areas. 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 "Health People 2000" (Summary Report: 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 underlying causes of 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 non-citizen nationals of the U.S. or its possessions or territories or must have been lawfully admitted to the U.S. for permanent residence at the time of application.

This non-renewable award provides support for a three-year period for individuals engaged in full-time research and related activities. Awards will not exceed \$50,000 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 non-citizen U.S. nationals 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 disease: asbestosis, byssinosis, silicosis, coal workers' pneumoconiosis, lung cancer, occupational asthma
- Musculoskeletal injuries: disorders of the back, trunk, upper extremity, neck, lower extremity: traumatically induced Raynaud's phenomenon
- Occupational cancers (other than lung): leukemia, mesothelioma, cancers of the bladder, nose and liver
- Severe occupational traumatic injuries: amputations, fractures, eye loss, and lacerations
- Cardiovascular diseases: hypertension, coronary artery disease, acute myocardial infarction
- Disorders of reproduction: infertility, spontaneous abortion, teratogenesis
- Neurotoxic disorders: peripheral neuropathy, toxic encephalitis, neuroses, extreme personality changes (exposure-related)
- Noise-induced loss of hearing
- Dermatologic conditions: dermatoses, burns (scalding), chemical burns, contusions (abrasions)
- Psychological disorders: affective disturbances such as anxiety, depression and job dissatisfaction; maladaptive 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
- Respirator research: new and innovative respiratory protective devices, techniques to predict performance, effectiveness of respirator programs, physiologic and ergonomic factors, medical surveillance strategies, psychological and motivational aspects, effectiveness of sorbents and filters, including chemical and physical properties

I. INCLUSION OF MINORITIES AND WOMEN IN STUDY POPULATIONS

Applicants 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). State and local government applicants may use Form PHS-5161-1 (revised 7/92); however, Form PHS-398 is preferred. 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:

<u>Receipt Date*</u>	<u>Initial Review</u>	<u>Secondary Review</u>	<u>Earliest Possible Start Date</u>
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

<u>Receipt Date</u>	<u>Initial Review</u>	<u>Secondary Review</u>	<u>Earliest Possible Start Date</u>
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 (CFDA)

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 "OH-923" 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 – 03/31/93*
Funding Level: *\$161,237 (\$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 1×10^6 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 are being 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 m²/g. For crystalline silica and ferric oxide that had larger count median diameters, the surface areas were 4.3 and 10.8 m²/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. 3×10^6 cells were incubated with BaP-coated particles for 24 hours. The data indicate there are more nonextractable BaP metabolites in the media with crystalline and precipitated silica > ferric oxide > fumed and gelled compared to BaP alone. The nonextractable metabolite distribution in the media is consistent with the metabolite profile in the extractable fraction in that the metabolites are greater for crystalline, precipitated and ferric oxide than fumed and gelled. The 9,10-dihydrodiol of BaP is substantially greater for the crystalline silica. So far, these data indicate that the smaller the surface of the particles the more BaP metabolic products are present in the media.

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 thus far indicate that qualitatively BaP-coated crystalline silica produces a greater level of binding of two major BaP adducts than BaP alone or BaP-coated ferric oxide. These data are consistent with the metabolic activation of BaP-coated crystalline silica described above. Work is presently ongoing to assess the adduct levels for all of the particles. However, it is significant that adducts have been detected for the first time in hamster AM by this method.

Publications

Griefe A, Warshawsky D: Influence of Dose Levels of the Cocarcinogen Ferric Oxide on the Metabolism of Benzo(a)pyrene by Hamster Pulmonary Alveolar Macrophages in Suspension Culture. *J Toxicol Environ Health*, accepted, 1992

Pilot Project to Assess Mortality Among Former Chromium Smelter Workers

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Grant Number: *5 R01 OH02298-02*

Start & End Dates: *07/01/89 - 06/30/92*

Funding Level: *\$34,068 (\$129,954 Cum)*

Importance to Occupational Safety and Health

The potential carcinogenicity of chromates was first reported in the German literature in the 1930's. The first health study of workers in the United States was reported in 1948. This study of workers in all the plants in the United States where chromates and bichromates were made from chromite ore (four in New Jersey, one in New York, one in Ohio, and one in Maryland) found that 22% of all deaths were due to cancer of the respiratory system. The Public Health Service studied these same plants in the early 1950's. A majority of the workers had perforated nasal septums (57%) and there was a 29-fold increase in deaths from respiratory cancer. Black workers had higher morbidity and mortality. Seventy-seven percent of the black workers had perforated nasal septums versus 50% among white workers. There was an 80-fold increase in deaths from lung cancer among black workers versus 15-fold increase among white workers. Prevalence of smoking among black and white workers was similar, 84% and 81% respectively. There were more heavy smokers among whites versus blacks (32% versus 12%).

More recent studies of the workers at the plant in Maryland have shown reduced risks of lung cancer with latter year of hiring. How much of the decreasing risk of lung cancer among workers in this plant with latter year of hiring can be attributed to improvements in working conditions with decreased exposure versus inadequate time from first exposure to evaluate the full risk of lung cancer among more recent hires cannot be determined.

Subsequent to these studies, all seven plants have closed. The Maryland plant, which closed in the mid-1980's, was the last of these plants to close.

Two new facilities have opened in North Carolina and Texas.

The Public Health Service concluded its report in 1953 by recommending: "It is recommended that all employees who have worked 5 years or more in the chromate industry should be x-rayed every 3 months, and their films should be read by a competent roentgenologist. The study of the morbidity and mortality experience of workers in chromate plants should be continued. The local health department should follow-up chromate workers who have worked in the industry 5 years or more."

No such follow-up was instituted until our project was initiated. Included in our study are the four original New Jersey plants and the new plant in Texas.

Objectives

1. Mortality study.
2. Determination of the feasibility of locating former workers and enrolling living workers in an early detection program for lung cancer.
3. High risk notification.

Methodology

The cohort was compiled from Social Security Administration "941" forms that are submitted by corporations on a quarterly basis. These forms contain a worker's name, social security number, and the employer's quarterly contribution on that worker to Social Security.

Quarterly Social Security records for the following dates were obtained: Plant A, 1948 until its closure in 1954; Plant B, 1948 until its closure in 1971; Plant C, 1937 until its closure in 1964; Plant D, 1937 until its closure in 1954; and Plant E (new plant in Texas), 1957 until 1964. A total of 5,104 workers were identified. The only activity at plants A-D was the production of chromates. Chromate production is only a part of the activity at Plant E. Because of this, the 1,696 workers from plant E have not been included in the mortality study. The quarterly records were used to determine duration of employment. The following sequential steps were taken to trace individuals (individuals did not receive a second contact if they responded to a previous contact, nor were the next of kin of deceased individuals contacted): (1) Identification of deceased individuals from Social Security and other governmental records provided to outside commercial firms; (2) A mailing by the Internal Revenue Service (IRS); (3) Identification of additional dead individuals from New Jersey Death Tapes; (4) A mailing to individuals who filed New Jersey income tax forms; (5) Placement of three newspaper advertisements in Texas; (6) A second mailing by the Internal Revenue

Service; (7) Identification of addresses by the Social Security Administration of individuals or dependents receiving benefits; (8) Identification of phone numbers in the local phone book from city where the Texas facility is located; (9) New Jersey motor vehicles records; and (10) the National Death Index.

Significant Findings

The findings of plant E are not included in the following discussion.

Despite the lack of current addresses, we have been able to determine the vital status and locate 83% of the cohort. We do not know for sure if the 17% of the cohort we were unable to locate are deceased or if they were notified and chose not to respond. Among workers who had worked more than 1 year we were unable to locate 9%. However, since we used data from Social Security, the National Death Index, and New Jersey computerized death tapes we believe that the majority of workers we were unable to locate are alive.

Over half (52.3%) of the cohort has died. Lung cancer was increased and is the cause of death in 13.6% of the members of the cohort. Analysis by duration, latency since first hire, time since leaving work and race still needs to be performed. We will be able to determine if workers, years after leaving work, are still experiencing an increased risk of lung cancer.

Seven hundred ninety (23.2%) of the former workers have completed a questionnaire. This represents 49% of the workers who are potentially alive. Sixty four percent of the workers who had worked more than a year who are potentially alive completed a questionnaire. Among all the workers who responded, 14% still smoke cigarettes, another 56% had quit smoking. Thirty one percent reported they had a perforated nasal septum.

A survey of a sample of the responders showed that 83% were glad they were notified, 17% unsure and 1% wish they had not been notified.

We are planning to notify the workers located of the results of the mortality study and to work with members of this cohort to offer them an opportunity to participate in a program to test early detection techniques for lung cancer.

Effect of Particle Load on Alveolar Clearance

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Program Area: *Occupational Lung Diseases*
Grant Number: *2 R01 OH02332-04*
Start & End Dates: *01/01/87 – 05/31/92*
Funding Level: *\$163,262 (\$569,878 Cum)*

Importance to Occupational Safety and Health

A number of occupations expose workers to high levels of aerosolized particulates. Mining, sandblasting, milling, alloy manufacturing, and employment in quarries and auto body shops are representative of such occupations. Whereas some particulates such as asbestos may directly injure cells which attempt to phagocytose them, other particulates are relatively inert, yet they may trigger lung injury when inhaled at high levels. Our research will establish the doses of inhaled inert particles which initiates impairment in lung clearance. This particle dose will be evaluated with respect to particle size by employing challenges with both supramicron and submicron particles. It is expected that impairment will occur at a different particle dose for each particle size. Additionally, macrophage-particle interaction with respect to cell activation, secretion of mediators after particle phagocytosis and cell-cell communication are to be studied for effects on lung clearance and initiation of inflammation.

Objectives

In the first years of our study we developed a number of techniques in a large animal, the sheep, to study particle clearance from the upper airways alveoli. In the last years we have extended the scope of investigations to particle-cell interactions under low and high particle burdens in the sheep lung. These cellular studies are designed to elucidate the mechanisms that promote chronic inflammation and fibrotic lung disease. The fibrotic lung diseases, as chronic inflammatory disorders, result in altered alveolar structures and deposition of connective tissue elements. The development of fibrosis seems to relate primarily to processes which subvert repair and promote inflammation. The alveolar macrophage with the capacity to recruit and activate other

inflammatory cells can be a central factor in subverting normal repair and initiating chronic inflammation. Our data indicate inhalation of high numbers of particles serve to activate the macrophage and impair its mobility. The concurrence of these events via inhalation of particulates would have chronic inflammation as an outcome. These studies may determine the mechanistic disordering induced by particulates. Of particular importance is paracrine modulation of other cells, whereby a smaller number of particle loaded macrophages activates a larger number of macrophages and other inflammatory cells resulting in diffuse chronic inflammation and fibrosis.

Methodology

Our approach will permit us to determine cell properties and clearance under low load and examine alterations in cell function and clearance under increasing lung burdens of supramicron and submicron particles. These particles will contain either a radioactive tag (^{57}Co) or a fluorescent tag. We will follow clearance non-invasively via gamma camera imagery and serial computer stored images. We will perform serial upper airway lavage and bronchoalveolar lavage. These cells will be examined for radioactivity by well counter and for particle content by fluorescent microscopy. The collected cells will be cultured and examined for surface receptors by fluorescently tagged antibodies. Changes in functional characteristics will be investigated such as increased O_2 consumption, pro-inflammatory and cytotoxic activity, phagocytizing capacity and paracrine mechanisms will be investigated by a variety of *in vitro* assays. Increasing particle loads administered by instillation and inhalation followed by gamma imagery and serial lavage will be evaluated for alterations in clearance and cell functions as outlined above.

Significant Findings

1. On instillation, 35% of the tracheobronchial macrophages contain both 0.5 μm particle and 3.0 μm particles at 1 hour post-deposition. The ratio of 0.5 μm particles to 3.0 μm particles engulfed by macrophages was the same as the number of particles deposited (400:1). No particles were found in tracheobronchial macrophages 48 hours post-deposition indicating upper airway macrophages had cleared within 48 hours confirming the non-invasive imagery of finding 1.
2. Particle phagocytosis results in a change in surface $\text{Fc}\gamma$ receptors, a parameter associated with cell activation. After particle phagocytosis *in vitro* the HMDMs appear to down regulate $\text{Fc}\gamma\text{R III}$, however, after 24 hours the levels

increase to above control levels. After particle phagocytosis *in vivo* increased immune complex FcγR were found on sheep AM's obtained 30 days post instillation.

3. HMDMs and sheep AMs after particle phagocytosis modulate neighboring macrophages which have not phagocytized particles as evidenced by a redistribution of FcγR on the macrophages which have not phagocytized particles. This paracrine modulation appears to be focal since AMs recovered from another lobe in the same sheep did not redistribute FcγRs.
4. After submicron particle phagocytosis *in vitro* HMDMs release TNF which further "activate" particle-free HMDMs to release TNF. After submicron particle phagocytosis *in vivo* sheep AMs release a putative TNF.
5. AMs containing greater than 5 (3.0 μm) particles may have impaired mobility being unable to migrate to the mucociliary escalator. AMs with less than 5 particles appear to be able to migrate to the escalator although the % of CAMS containing 1 to 5 (3.0 μm) particles was considerable less than the % of AMs on each of the serial bronchoalveolar lavages (BALs). This indicates that AMs may have some level of impairment even after phagocytizing fewer than 5 particles. The significant difference in particle retention between low and high burden indicates that large numbers of particles impair macrophage mediated alveolar clearance.

Publications

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Langenback EG, Bergofsky EH, Simon SR, Halpern JG, Foster WM: Normal Macrophage Turnover Rate in the Sheep Lung. *Am Rev Respir Dis*, 1991 (Abstract)

Langenback EG, Bergofsky EH, Simon SR, Halpern JG, Foster WM: Particle Distribution in Alveolar Macrophages in Serial BAL after Particle Inhalation and Instillation in the Sheep. *Am Rev Respir Dis*, 1991 (Abstract)

Jain P, Brown EJ Jr., Langenback EG, Raeder E, Lillis O, Halpern JG, Mannisi JA: Effects of Milrinone on Left Ventricular Remodeling After Acute Myocardial Infarction Circulation. 84:796-804, 1991

Dulchavsky SA, Kennedy PR, Geller EF, Foster WM, Langenback EG: T₃ Preserves Respiratory Function

in the Rodent Model of Sepsis. *J Trauma* 31:753-759, 1991

Jain P, Mallavarpau C, Mannisi JA, Lillis O, Langenback EG, Raeder E, Halpern J, Brown EJ, Jr.: Milrinone Prevents Infarct Scar Thinning: Evidence for Late Infarct Zone Remodeling. *Am Heart Assoc*, 1991 (Abstract)

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

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

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

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

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

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

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

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

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

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

Lung Disease in Chinese Textile Workers

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Program Area: *Occupational Lung Diseases*
Grant Number: 5 R01 OH02421-03
Start & End Dates: 07/01/91 - 06/30/95
Funding Level: \$89,930 (\$284,587 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 FEV₁ 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 FEV₁ at baseline screening and subsequent development of respiratory symptoms and loss of FEV₁.

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 were contacted and tested at year 5 and will also be at year 11. The cause of death, as well as other reasons for loss from cohort, has been ascertained on all subjects.

Significant Findings

Data collection for the 11-year follow-up is to be completed by December, 1992. Ninety to ninety-five percent follow-up is expected.

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 FEV₁ over 5 years; (4) cotton-exposed workers, but not silk workers, with a greater than or equal to across-shift loss in FEV₁ at the time of first survey had significantly greater 5-year loss in FEV₁ after appropriate adjustments.

Publications

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, 1992

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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

Airway Hyperresponsiveness Due to Cotton Dust

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Program Area: *Occupational Lung Diseases*

Grant Number: *2 R01 OH02593-03*

Start & End Dates: *09/01/89 - 08/31/95*

Funding Level: *\$141,998 (\$409,153 Cum)*

Importance to Occupational Safety and Health

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

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

Objectives

Our specific aims are:

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

Methodology

Our laboratory has developed an *in vivo* model for studying the effects of cotton dust on human airways. The model consists of studying lung function changes resulting from challenge with an aerosol containing the water soluble extract of cotton bracts (CBE). The two major objectives of the current study will be examined using this model.

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

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

Significant Findings

We exposed 27 healthy non-smokers (NS) to CBE inhalation on 5 consecutive days; and on a 6th day, following a 2-day interruption of CBE inhalation. Partial and maximal expiratory flow volume loops were obtained prior to (BL) and at 15 minute intervals for 2 hrs after CBE inhalation.

The average maximal MEF40(P) percent decrement from BL(AMMPDB) was calculated for each of the 6 days; the AMMPDB for each day was $19.8 \pm 3.1\%$ on day 1, $11.1 \pm 2.5\%$ on day 2, $10.5 \pm 1.9\%$ on day 3, $10.6 \pm 2.2\%$ on day 4, $9.4 \pm 1.9\%$ on day 5 and $17.7 \pm 3.4\%$ on day 6. Longitudinal

data analysis, comparing the AMMPDB from day 1 with the AMMPDB from each of the subsequent days revealed that the AMMPDB was greater on day 1 than on subsequent weekdays ($p=0.002$). No significant difference in AMMPDB was noted between day 1 and day 6. No significant difference in AMMPDBs was noted between non-Monday days ($R^2=0.446$ for days 1 and 6). Conclusion: (1) Acute decrements in expiratory flow-rates were observed following sequential daily challenges with CBE of cotton bract extract, (2) daily decrements in expiratory flow rate following inhalation of CBE on 5 consecutive days were greatest on the first day, (3) after a 2-day interruption of CBE inhalation, CBE induced decrements in expiratory flow rate return to levels noted on the first day of CBE inhalation.

We studied the response to methacholine challenge (MC) at baseline (BL) and 2 hrs. after the inhalation of nebulized CBE in 50 healthy smokers (HS) (mean=11 $\pm$ 9 pack years) and 28 healthy nonsmokers (HNS) ages 18-40. Partial and maximal expiratory flow volume loops were obtained prior to bronchial challenge (BL); at fifteen minute intervals following CBE inhalation; and after each inhaled incremental dose of MC up to a maximal dose of 200 mg/ml.

In 9 of 28 HNS versus 27 of 50 HS, a $> 20\%$ decrement in MEF40(P) occurred within 2 hours of CBE inhalation. The mean BL MC log (PD20MEF40(P)) +1 was significantly lower in Smokers vs Non-smokers, 1.8 vs 2.7 ($p<0.001$). Two hours after CBE inhalation, no significant change in bronchial responsiveness to methacholine was noted in the HNS but was seen for HNS responders ($p<0.001$). In the HS, a lower log (PD20MEF40(P)) +1 for methacholine was noted after CBE challenge; 1.5 ± 1.1 ($p<0.01$). At 2 hours after CBE inhalation, the response to methacholine was lower in smokers vs non-smokers ($p<0.001$). Conclusion: (1) Young HS have a higher response rate to CBE induced flow changes than HNS; (2) CBE enhances airway reactivity in HS; (3) HS exhibit greater bronchial responsiveness than HNS to methacholine both at BL and 2 hrs after CBE inhalation. (4) HNS responders exhibit hyperreactivity following CBE.

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A Rational Method for Sampling Airborne Fibrogenic Dust

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Importance to Occupational Safety and Health

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

Objectives

The objective of this project is to develop a new dust sampling device, with performance characteristics that are as close as possible to actual pulmonary deposition (PD), to alleviate the limitations described above. The device consists of a 10 mm cyclone followed by a single-nozzle one-stage impactor. The dust fraction of interest is collected by impaction on 10 mm diameter microscope cover

slips. Theoretically, estimation of PD is obtained by selecting the appropriate air flow rate and diameter of impact or so that the combined performance of the impactor and cyclone will simulate the bell shaped curves of PD at various RF and TV. Six single-nozzle impactors are used with jet diameters of 0.139, 0.159, 0.179, 0.198, 0.218, and 0.238 cm. This configuration was selected, rather than two impactors in series, to obtain better matching of PD (impactors have sharp and steep cut-off curves as compared to cyclones). A cyclone can also collect large amounts of dust without overloading. Other potential advantages of the instrument include reduced handling steps for chemical analysis of the collected dust, e.g., a silver membrane filter may be used as the collection stage for silica. This filter can be directly submitted for x-ray diffraction analysis. Performance of the new sampler is evaluated using aerosols with aerodynamic equivalent diameters ranging from 0.5 to 10 μm at air flow rates within the range of battery-operated personal sampling pumps (0.5 to 3.0 lpm).

Methodology

Two types of aerosols are used in this study, polystyrene latex (PSL) monodispersed particles and uranine-methylene blue (UMB). The UMB solution is produced by dissolving uranine and methylene blue in the ratio of 2:1 by weight in an aqueous solution of 40% ethyl alcohol. The UMB and PSL particles $>3 \mu\text{m}$ in diameter aerosols are generated using a May Spinning Top aerosol Generator with a Harvard syringe pump model 931 to feed the solution to the generator. Satellite aerosol is removed using a high volume EG&G Rotron blower model SL4P2. PSL $<3 \mu\text{m}$ are generated using a Colison nebulizer. The generated aerosol is delivered to the top of a 21 ft³ aerosol sampling chamber through a TSI Inc. Kr-85 particle neutralizer model 3054. The aerosol is thoroughly mixed with dilution air at the top of the chamber before it is allowed to pass through a diffusion screen to the sampling compartment of the chamber. The air is exhausted from the sampling compartment through another diffusion screen by the same EG&G blower. Particle size distributions for the UMB are determined by microscopy and a density of 1.4 mg/cm³ is assumed for the conversion of projected area diameters to aerodynamic equivalent diameters. Control of the size of the generated aerosols is achieved by the selection of the appropriate concentration of UMB used in the generation solution. A UV/VIS spectrophotometer is utilized for all UMB mass determinations. PSL sizing and counting are obtained using a HIAC/ROYCO particle counter model 4100.

Significant Findings

Performance of the 10 mm nylon cyclone and two European types of metal cyclones (the first is marketed by SKC and the second by BGI, Inc) utilized for personal sampling of respirable dust were also evaluated at air flow rates of 0.5, 0.75, 1, 1.5, 2 and 3 lpm. The penetration characteristics of the aluminum cyclones were consistently higher than those of the nylon version. The health implications of these findings, that is, over estimation of the inhaled dose, may be looked upon in two ways. The first case, utilization of these metal cyclones in epidemiologic studies of pneumoconiosis will result in dose-response relationships that underestimate the toxicity of the agent. The second case is when dust sampling is performed for compliance purposes, where the results over estimate the worker's exposure or erring on the safe side, that is, protection of the workers' health. The 50% cut-off at 3.5 μm is obtained at 1.9 and 2 lpm for SKC and BGI cyclones. Calibration of the 6 impactors indicates that their effective cut-off diameters are 1.61, 1.94, 2.32, 2.7, 3.12 and 3.56 μm . The results obtained to date show that the basic concept of the proposed instrument is valid but the actual performance of the instrument is significantly different from that obtained by combining the individual theoretical performance of each component. The actual performance of the cyclone in series with the single stage impactor results in a very steep slope in comparison to the predicted theoretical values. The objective of this project could be achieved using cyclones with collection characteristics lower than those available at the present time.

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Coal Dust Particle Size and Respiratory Disease

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Importance to Occupational Safety and Health

Exposure to coal mine dust is strongly associated with the development of coal workers' pneumoconiosis (CWP) and chronic obstructive lung disease including emphysema and chronic bronchitis. The most important studies which demonstrate such effects use measurements of respirable coal mine dust, i.e., dust depositing primarily in the terminal airways and alveoli as the basis of their exposure assessment. There are, however, good reasons to believe that chronic bronchitis may be more specifically associated with exposure to larger particles of dust which deposit in the tracheo-bronchial tree. This study will examine the independent effects of respirable and tracheo-bronchial dust fraction 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 exposures will be 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 compared 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 miners. 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 exposure over time was also developed that accounts for non-linear effects of exposure concentration and time since exposure.

Significant Findings

Analysis of personal cascade impactor studies from four mines suggest that the variability of particle size distributions within occupations is as great or greater than variability between occupations. The findings suggest that epidemiologic analyses based on respirable dust measurements are equally as effective as tracheo-bronchial measures for the study of chronic disease. However, it is still possible that individual measurements of tracheo-bronchial dust exposures might be more effective in reducing the risk of lung disease.

A new metric for the summarization of chronic exposures across time has been developed and used for the association of respirable dust exposure and obstructive lung disease outcomes. The metric includes exponential weights for dust concentration and time since exposure and allows the epidemiologic data to determine the optimal exponents for the expression. The results indicate that the assumptions built into simple cumulative exposure may not be appropriate for these outcomes and suggests that alternative weighing schemes may improve the ability

of epidemiologic data to determine low level associations.

Publications

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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/cm³ and clearance could cease at 30 mg/g lung. Under reasonable assumptions for the deposition rate and clearance halftimes 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/m³, 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 TiO₂ 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

The magnetometry system for small animals has been assembled and successfully tried on rats and the nose-only inhalation exposure with restraining tubes was mastered using single or repeated exposures of magnetite alone and of a mixture of magnetite with TiO₂.

Magnetometric results clearly show the increase in lung burden during exposure and also clearance of magnetite particles after the exposure was discontinued. This was expected. Clearance of particles based on magnetometry measurements

seemed to be unexpectedly fast ($T_{1/2} = \sim 20$ days). However, based on chemical analysis magnetite clearance was as expected slower ($T_{1/2} = \sim 150$ days). Correlation of the lung burden magnetic signal with the chemical analysis of iron in the pulmonary tissue showed no linearity in the post-exposure period. The magnetic signal seems to be affected by some post-exposure processes which we think are related to particle relocation within the lung tissue. The results with respect to clearance were similar after single or after repeated exposures and between magnetite and TiO_2 particles determined chemically. We are now in the process of clarifying these findings in order to develop correction factors using *in vivo* and *in vitro* experiments. This clarification may be decisive for the practicality of using magnetometry in human studies.

In another experiment, rats were irradiated (thorax only) before particle exposure. The aim was to decrease and affect the pulmonary alveolar macrophages (AM) and their alveolar clearance functions. The compromised AM may change the pulmonary tissue response at the time of exposure to magnetite which may show in the magnetometric results. It seems that the "non-relaxing (15 min.)" fraction of the lung burden is not AM-dependent as hypothesized by some, based on *in vitro* indirect results of the past.

Publications

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On-Site Enumeration of Fungal Spores and Bacteria in Air

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Importance to Occupational Safety and Health

The analysis methodology is expected to yield a measure of exposure to viable and nonviable bioaerosols that have been implicated in the development of lung diseases, such as hypersensitivity pneumonitis (HP). The developed methodology will allow timely on-site analyses which will facilitate the correlation of currently observed symptoms with exposure conditions. Timely analyses will also facilitate the development and interpretation of comprehensive sampling strategies. Sequential sampling 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 and work activities with exposure. The determination of individual exposures will be possible.

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 visible and epifluorescent microscopy after supravital staining the spores and bacteria.
2. The primary goal of the first year of study will be 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.
3. In the second year, an air sampling device will be fabricated to collect primarily thoracic particles (i.e., those particles that pass beyond the head and neck during breathing). Test atmospheres of a nonbiological fluorescent aerosol and representative fungal spores and bacteria will be 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

Suspensions of spores and bacteria have been added to filters and examined microscopically without fixation as originally proposed. The suspensions have been prepared from freeze-dried preparations, which are rehydrated in neutral buffered saline or in ISOTON II, the electrolyte used for Coulter counting, prior to being aliquoted to a filter. The bioparticles are stained by placing the loaded filter on a microscope slide, adding 5 to 10 μ L of 0.2 mM

understood are the pathophysiologic mechanisms responsible for subacute or chronic airway diseases resulting from repeated or persistent airway oxidant injury.

From the work of a variety of investigators, it has become clear that the airway mucosa produces a variety of factors in health or after oxidant injury that affect other airway cells. One such factor is so-called epithelial-derived relaxing factor (EDRF). Perhaps, its primary target is airway smooth muscle. It has been shown by numerous investigators, including ourselves, that denudation of the respiratory mucosa increases airway muscle responsiveness to a variety of bronchoconstrictors possibly due to the loss, in part, of EDRF. We have also reported that ozone-induced airway hyperreactivity which is unassociated with frank mucosal denudation pathologically, is associated with airway muscle hyperresponsiveness *in vitro* to various bronchoconstrictors, including tachykinins.

We believed the mechanisms responsible for this airway tachykinin hyperresponsiveness post ozone were particularly important to investigate, in that a variety of signs and symptoms of acute, oxidant-induced airway diseases may be ascribable to them. In our studies, we have found that ozone-induced, airway muscle tachykinin hyperresponsiveness is at least partly linked to ozone inactivation of another mucosal-linked factor, namely neutral endopeptidase.

Our laboratory was the first to report the effects of ozone and of hypochlorous acid (HOCl) on airway neutral endopeptidase (NEP). To test whether ozone-induced respiratory injury in guinea pigs was associated with inactivation of airway NEP and an increase reactivity to substance P, we assessed the influence on airway substance P reactivity of phosphoramidon, an antagonist of NEP. Reactivity after ozone or air exposure was determined by measuring specific airway resistance in intact, unanesthetized, spontaneously breathing animals in response to increasing doses of intravenous substance P boluses. We found that phosphoramidon significantly increased substance P reactivity in the air-exposed animals, but it had no effect in the ozone-exposed group. This finding was associated with a significant reduction in tracheal homogenate NEP activity of ozone-exposed animals compared to controls. Inhalation of an aerosolized NEP preparation, partially purified from guinea pig kidney, reversed the substance P hyperreactivity produced by ozone exposure. Inhalation of phosphoramidon post-NEP inhibited this effect. Heat inactivated NEP aerosol had no influence on ozone-induced hyperreactivity. These data indicated that ozone exposure decreases airway NEP activity and increases substance P reactivity which can be reversed by aerosolized NEP.

We have also demonstrated that luminal exposure of airway segments *in vitro* to the oxidant HOCl produces airway muscle hyperresponsiveness to substance P and a decrease in neutral endopeptidase (NEP) activity of tissue segment homogenates, suggesting that HOCl may decrease airway epithelial cell NEP activity. To confirm that this effect occurs in man and to investigate possible sub cellular mechanisms for it, we assessed HOCl exposure of the human airway epithelial cell line Calu-1. These cells, grown to confluency in Dulbecco's modified eagle medium with 10% fetal bovine serum, were exposed *in situ* for 5 min to 100 μ M HOCl in a phosphate buffered saline solution. Thereafter, cells were rinsed and assayed for NEP activity employing reverse phase, high pressure liquid chromatography (HPLC). Cell viability was assessed by changes in LDH release, trypan blue exclusion, and cell volume. In some experiments, crude plasma membrane and soluble components of exposed cells were isolated and differential NEP activity was assayed. We found that a 5 min exposure to HOCl significantly decreased whole cell NEP activity, while no parameter of cell viability was affected. NEP activity in the crude membrane fraction decreased after exposure, whereas NEP activity in the soluble fraction increased significantly. Isolated membrane NEP exposed by itself was not affected. From these experiments, we concluded that whole cell HOCl exposure decreases Calu-1 plasma membrane NEP, and we speculated that this loss occurs by internalization of cell membrane NEP.

To confirm these findings, and to assess the time course of changes in cell NEP after oxidant exposure and the potential influence of corticosteroid treatment on these, we have evaluated Calu-1 NEP activity and NEP-specific mRNA synthesis over the ensuing 48 h post-HOCl in the presence or absence of 1 μ M dexamethasone. (We have previously reported that dexamethasone increases both NEP activity and its steady-state mRNA in Calu-1 cells in a time- and dose dependent manner.) Prior to HOCl exposure, some cell plates were incubated for 5 min in 1 mM sodium azide. Thereafter, cells were rinsed free of the HOCl and then maintained in culture for 48 h. NEP activity was assayed employing HPLC. In some experiments, post-HOCl changes in NEP-specific mRNA in the presence or absence of dexamethasone were also evaluated employing Northern blot analysis. We found that sodium azide blocked the effect of HOCl on Calu-1 NEP. In the absence of sodium azide, NEP activity spontaneously recovered to pre-exposure levels within 24 hours. This recovery occurred 6 h earlier in the presence of 1 μ M dexamethasone. Furthermore, dexamethasone significantly increased NEP activity at 24 hours after HOCl exposure. Northern blot analysis indicated that NEP-specific mRNA did not change during

spontaneous recovery, but was increased by dexamethasone 24 h post-HOCl. From these experiments we concluded that HOCl exposure decreases Calu-1 plasma membrane NEP by inducing its internalization. Exocytosis of internalized enzyme may be responsible for the spontaneous recovery of cell surface NEP after oxidant exposure. This recovery is substantially accelerated by dexamethasone treatment which stimulates NEP-specific mRNA synthesis by these cells.

Recently, we have investigated whether dexamethasone pretreatment affected the acute increase in airway reactivity that is produced by high level ozone exposure. Reactivity to IV substance P (SP), IV acetylcholine (ACh), or aerosolized capsaicin (CAP) before and 1 h after ozone exposure (3 ppm for 2 hr) was determined by measuring specific airway resistance in anesthetized, spontaneously breathing guinea pigs, half of whom had been pretreated for 2 d pre-ozone with dexamethasone (2mg/kg IM qd). The amount of IV SP, IV ACh, or inhaled CAP necessary to increase baseline specific airway resistance by 100% (ED₂₀₀ACh or ED₂₀₀SP) or 35% (ED₁₃₅CAP), was determined by interpolation from dose-response curves. Compared to their pre-ozone status on the day of exposure, we found that dexamethasone pretreated animals manifested significantly less of an increase in airway reactivity post-ozone to IV SP or inhaled CAP than did untreated animals. Changes in log ED's of the pretreated group were 0.18±0.03 (mean±SE) for SP and 2.20±0.11 for CAP compared to 0.27±0.04 and 3.38±0.34, respectively, for the untreated groups post-ozone ($P<0.05$ and $n=4$ for each). In contrast, dexamethasone pretreatment had no effect on IV ACh reactivity post-ozone: changes in logED₂₀₀ ACh were 0.27±0.08 and 0.28±0.04 for the pretreated and untreated groups, respectively ($n=4$). In animals pretreated with captopril to block possible dexamethasone stimulation of angiotensin converting enzyme synthesis which could influence tachykinin reactivity, we found that the corticosteroid effect on post-ozone SP reactivity was as marked as that seen in animals without captopril ($n=4$). Because these reactivity studies were consistent with the possibility that dexamethasone may ameliorate ozone-induced, tachykinin hyperreactivity by stimulating airway neutral endopeptidase (NEP), we measured NEP activity by HPLC of each tracheal homogenate made from other groups of animals. Homogenates from ozone-exposed, dexamethasone pretreated animals demonstrated significantly greater NEP activity (81%±24%) than that from ozone-exposed, untreated animals ($P<0.05$, $n=5$). We therefore concluded that corticosteroid pretreatment reduces the acute increase in airway reactivity to exogenous and endogenous tachykinins caused by ozone. This reduction may be at least

partly due to stimulation of airway NEP activity, perhaps most of which is non-mucosal in that ozone acutely inactivates mucosal NEP. This steroid effect may benefit post-oxidant reactivity to both exogenous and endogenous tachykinins as our study suggests.

Based upon previously published data in subhuman species, it is suspected by some that repeated airway ozone exposure may result in epithelial hyperplasia and metaplasia. Given the recent observation that NEP is responsible for catabolizing BLP and endothelin, and our reports that airway epithelial NEP activity is dramatically decreased by ozone, and by oxidants such as HOCl, it is tempting to speculate that at least one of the causes of the increased BLP (including gastrin-releasing pep tide) in a variety of lung disorders is a decrease in airway epithelial NEP expression due to oxidative cell damage. On the basis of our NIOSH-sponsored work, we hypothesize that enhanced epithelial proliferation after repeated ozone exposure may derive, at least in part, from a persistent decrease in epithelial cell NEP expression, thereby subjecting the surviving and growing cells to unopposed stimulation by key mitogens such as GRP and endothelin.

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The Immunopathogenesis of Occupational Diseases Due to Reactive Chemicals

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Importance to Occupational Safety and Health

Reactive small molecular weight chemicals are recognized as important causes of occupational asthma and reactive airways disease. Occupational asthma has been associated with exposure to various types of chemical diisocyanates including toluene diisocyanate (TDI), diphenylmethane diisocyanate (MDI), and hexamethylene diisocyanate (HDI). It has been estimated that occupational asthma occurs in 5% of diisocyanate-exposed workers. The clinical presentations of diisocyanate asthma resemble other forms of immunologic asthma. However, specific IgE responses to relevant diisocyanate-human serum albumin (HSA) antigens have been identified in only 10% of symptomatic workers. As a result, other non-immunologic mechanisms have been postulated. *In vitro* lymphocyte proliferation after stimulation with specific TDI-HSA antigens have been documented in workers with TDI asthma, suggesting that cellular immunity may play a significant role. It was postulated that specific cellular immune responses to diisocyanates in sensitized workers could result in production of a cytokine mediator, histamine releasing factor (HRF) that could in turn activate effector cell populations, (i.e., basophils, mast cells) to release bioactive mediators (i.e., histamine). Refinement of *in vivo* methods that measure cellular responses to specific occupational antigens could allow development of assays which could identify affected workers or those at potential risk for development of diisocyanate asthma.

Objectives

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

The second objective of this study was to determine whether peripheral mononuclear cells from workers with diisocyanate asthma produced histamine releasing factors (HRF) after *in vitro* stimulation with diisocyanate-HSA antigens. The overall hypothesis of this study is that cellular immunity may play a central role in the elicitation of occupational asthma and that *in vitro* detection of such responses could serve as biologic markers.

Methodology

The population was to comprise 20 workers with exposure to MDI, of which 10 had been diagnosed with occupational asthma based on a physician history and 10 had been asymptomatic with no respiratory complaints. Relevant test antigens were prepared by coupling MDI, HDI, and TDI to HSA followed by complete chemical characterization of resultant conjugates. The MDI-exposed population was evaluated by intracutaneous and epicutaneous testing to MDI-HSA, TDI-HSA, and HDI-HSA. To detect specific humoral immune responses, serum samples were assayed with specific IgG (ELISA) and specific IgE (RAST) to MDI-HSA. A panel of *in vitro* cellular assays was performed in study subjects which included: (1) direct leukocyte inhibitory factor (LIF) assay in response to HSA conjugates of TDI, MDI, and HDI; and (2) an assay for histamine releasing factor (HRF) derived from supernatants of 18-hour peripheral blood mononuclear cell (PBMC) cultures after stimulation with MDI-HSA antigens. PBMCs were purified and cultured with MDI-HSA, TDI-HSA, HDI-HSA, HSA and T cell mitogens Con A and PHA. Supernatants were tested for HRF activity on normal non-atopic donor basophils.

Significant Findings

During the 3 years of this project, 18 diisocyanate workers have been recruited and screened. Ten of the latter individuals presented with prior histories of wheezing and dyspnea temporally related to MDI exposure. Challenge tests to MDI were able to be performed in 8 subjects, of which 5 were found to be positive. HRF activity was analyzed in the following

groups: Group 1 OA confirmed by specific bronchial challenge (n=5); Group 2 suspected OA with negative challenge (n=3); Group 3 suspected OA no challenge performed (n=2); Group 4 asymptomatic MDI exposed workers (n=8); Group 5 Non-atopic controls not exposed to diisocyanates (n=2); Group 6 Subjects with respiratory sensitization to unrelated (non-diisocyanate) antigens (n=3). In 5 symptomatic workers who exhibited significant HRF activity, cross sensitivity to other diisocyanate-HSA antigens was demonstrated. Spontaneous mean HRF production was significantly greater in the group with confirmed OA (n=5) compared to all other available subjects (n=16). HRF release to specific diisocyanate antigens was significantly greater in the group with confirmed OA compared to the asymptomatic diisocyanate exposed group (n=8) (p<.05). HRF production was demonstrated in all subjects to Con A or PHA. The diisocyanate specific HRF production was not related to serum specific IgE or IgG production. A leukocyte inhibitory factor assay was performed in 11 workers who reported symptoms. Five workers exhibited significant inhibitory responses in response to diisocyanate HSA antigens. Among 6 subjects in whom results were available for the both LIF and HRF assays, 3 exhibited concordance (positive responses to both assays) and 3 had discordant results. *In vivo* skin testing performed with HSA conjugates of TDI, MDI, and HDI were negative in all symptomatic subjects. Serum specific IgE to MDI, TDI, and HDI-HSA was not detected in symptomatic or asymptomatic workers. Elevations in specific IgG to diisocyanate HSA by the ELISA assay was detected in only 5 of 19 subjects, and there was no apparent relationship between specific antibody responses and positive responses to diisocyanate antigens in LIF and HRF assays.

The data indicate that histamine releasing factor (HRF) activity in response to specific antigens could be identified in 5 symptomatic individuals with positive challenge tests. This study suggests *in vitro* production of antigen specific cytokines (i.e. HRF) may serve as useful markers of occupational immunologic asthma.

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Effects of Zinc Oxide Welding Fume Inhalation

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Importance to Occupational Safety and Health

The self-limited systemic illness associated with zinc oxide fume inhalation suggests a flu-like illness: malaise, myalgia, and fevers in the range of 38 to 39 degrees. The mechanisms underlying zinc induced MFF have not previously been elucidated. Recent animal and limited human data indicate that zinc oxide fume inhalation results in marked pulmonary cellular inflammatory response. This suggests that the lung may be more than merely a conduit for exposure, instead playing an important role in 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 is that the effects of zinc oxide fume inhalation are mediated by cytokines. To study this hypothesis, we examine 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 study 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.

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 have previously published analysis of the first 14 subjects (5 early and 9 in the late follow-up groups). Among the late follow-up group, the four subjects with the highest cumulative exposures (all greater than 3.5 gmin/m^3) all experienced myalgia during the night following exposure and prior to bronchoscopy. We sampled for other metals associated with metal fume fever or pneumonitis that may be found in welding environments and documented that higher than trace concentrations were not present. 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 mean of $37\% \pm 18\%$ (range 19 to 63%). The mean proportion of polymorphonuclear leukocytes among the early follow-up group was $9\% \pm 8\%$ (range 2 to 21%). This proportion was statistically less than that of the late group ($p=0.005$). There was a strongly positive correlation between cumulative zinc oxide welding fume exposure and polymorphonuclear leukocyte concentrations both at 8 and 22 hours follow-up. The mean absolute increase in blood polymorphonuclear leukocytes among the late follow-up group was $4.9 \pm 2.4 \times 10^3/\text{mm}^3$ (eight subjects only) and was statistically significant (95% CI 2.6 to $7.2 \times 10^3/\text{mm}^3$). There was also an increase in peripheral polymorphonuclear leukocytes among the early follow-up group of $1.4 \pm 2.5 \times 10^3/\text{mm}^3$, although this change was not statistically significant (95% CI -1.7 to $4.4 \times 10^3/\text{mm}^3$). Cumulative zinc dose was significantly correlated with the increase in peripheral polymorphonuclear leukocytes in the late follow-up group ($r = 0.77$; $p = 0.02$).

Our 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 have now 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 begun to study 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. We intend to pursue this arm of the study further as well as carrying in vitro studies of macrophages exposed to zinc oxide.

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Asbestos-Induced Pleural Fibrosis and Lung Restriction

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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 ($\text{VO}_2 \text{ Max/kg}$) ($p=0.005$) 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 $> 1/0$) was present in 40% of those with normal pleura, 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 $A-a \text{ O}_2$ 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 asbestos is (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.

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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 approximately 70% of the general public who do not smoke.

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. environmentally-exposed home residents.

Methodology

(1) Analyze previously-collected biological data to quantify how the relative biological hazard varies with LET (Linear Energy Transfer, or stopping power) and its microdosimetric correlate, lineal energy. Only biological measurements pertinent to risk estimation, namely oncogenic transformation, mutation, and chromosomal damage, are considered; (2) use Monte-Carlo simulation of alpha-particle transport, together with the best available data on mucosal and epithelial thicknesses in smokers and

non smokers, 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

We have calculated microdosimetric spectra as a function of depth in the bronchial epithelium, as a function of (a) different assumptions as to how the polonium source particles are distributed within the bronchial mucosal layer and (b) different assumption about the relative weights of the two significant isotopes, ^{214}Po , and ^{218}Po , in both domestic and miner situations. We have also investigated the importance of energy deposition from alpha particles arising from the far side of the bronchial airway, and have concluded that the effect on relative biological effect will be small.

We have calculated biological response functions as a function of lineal energy deposition for endpoints of cellular inactivation in three different cell lines, mutation at the HPRT locus in two cell lines, chromosomal aberration formation in two cell lines, and oncogenic transformation in two systems.

We have folded these biological response functions with the calculated microdosimetric spectra for the case of domestic exposure. An average Q value of around 25 has been estimated for the domestic exposure situation, and corresponding calculations for the miner situation are in progress.

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 discordant 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. Data from the validation process illustrates the followings:

1. For most of the joints, the predictions and the actual motion patterns are very close to each other. The shoulder joint is the only joint with higher deviation, and may be explained by the upper arms' abduction, adduction, and rotation. The assumption of the rigid trunk link also contributes to the errors of shoulder and hip joints.
2. Phase relationships, evaluated by the discordant pairs, can be found in the graphical comparisons. Since the model assumed that all joints maintain stationary at time 0 (before the box is lifted off of the ground), any movement initiation before time 0 can not be predicted and any delay may contribute to the phase relationships. Model refinements are being implemented to account for phase relationships.

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Back Injuries in Municipal Employees

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Importance to Occupational Safety and Health

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

Objectives

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

Methodology

The study population was comprised of 200 cases and 400 controls from the four departments identified above. Data were collected during the period March 1, 1990 through April 30, 1991. Cases were identified by the study coordinator in the

Occupational Medicine Clinic from the injury reports, clinic reports and medical records. The controls were identified through the four departmental personnel offices. Information about the cases and controls was relayed to Survey Research Associates (SRA) to conduct the in-person interviews. Data collected from cases and controls included: psychosocial and work organization factors, work history, history of back pain, history of injuries, ergonomic factors, health behaviors, medical conditions, anthropometric measures, and perceptions about prevention of low back injuries. In addition, data were collected from the cases about the day of injury and circumstances of the low back injury.

A 10% sample of the cases had a site visit to verify the ergonomic data collected by interview and to discuss ideas for preventive interventions with the workers.

Data were analyzed to identify risk factors associated with low back injury using multivariate techniques. Site visit data were compiled to recommend specific ergonomic preventive strategies.

Significant Findings

1. Twenty-six percent of the low back injuries were related to motor vehicles; 24 percent to lifting activities, 18 percent to slips and falls; and 32 percent were due to other circumstances.

The most common circumstances of injury were related to motor vehicle impacts (51 cases); slips including slipping and falling from vehicles (36 cases); lifting trash cans (18 cases); and other lifting (29 cases).

2. The risk factors associated with low back injury among municipal workers include the following:

Variable	Relative Odds	p-value
High job strain	2.1	.004
Medium job strain	1.7	.011
Body mass index	1.04	.017
Work movement index	1.4	.068
Age (1 yr. increment)	0.98	.076

3. From the factors listed above, preventive strategies could be directed at the following: job strain, work movements (stooping, twisting and extended reaching), and personal weight reduction.

Recommendations from the site visits and worker input included the following suggestions to reduce injury: (some selected examples)

- (a) Motor vehicle injuries
 - * Keeping seat belts readily available and clean, providing one for each occupant.
 - * Padding the seats of trucks and tractors with energy-absorbing materials to reduce the exposure to impact and vibration.
 - (b) Lifting trash cans
 - * Limiting the size of trash cans.
 - * Placing a weight limit on loaded trash cans.
 - * Using a load packer rather than a lift-pack truck, which requires workers to lift cans higher.
 - (c) Other lifting
 - * Mechanized lifting equipment on trucks.
 - * Having a tailgate that allows rolling things into trucks.
 - * Providing wheelbarrows rather than requiring bags of cement to be carried.
 - (d) Other events
 - * Locate condensing units or other equipment requiring repair so they are accessible without crawling, stooping, etc.
4. Ergonomic analyses showed that: (a) the majority of overexertion injuries were attributed to one of the three most strenuous tasks described within the questionnaire, (b) both the coworker and job classification controls presented similar descriptions of the severity of physical work performed by municipal workers within their respective departments, and (c) reports of frequencies and duration of exertions deemed strenuous were also similar.

Within a given worker, descriptions of the most strenuous tasks were usually consistent with collateral descriptors of posture, hand force directions, and other metrics describing the work activity. However, workers often showed significant errors in describing the magnitude of hand forces required to perform the task. These errors required on-site measurements and corrections prior to conducting any biomechanical or NIOSH WPG analyses. Detailed presentation of analyses and outcomes of reliability and validity tests of the questionnaire's ergonomic sections are provided in Wiker and Jones, 1992.

Publications

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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 over a period of one month. 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. Little is known about this unique type of muscle response. In addition, the non-muscle tissue of these strained muscles proliferates as one might see in scar tissue. This additional non-muscle tissue may: (1) alter the action of muscles as motors decreasing their force or ability to shorten at maximal speeds; or (2) decrease the nutrient flow necessary to maintain dynamic or static activities over a long period such as occurs during assembly line work. 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); and (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.

Methodology

Cumulative microtrauma is administered three times a week for four weeks using our manual strain protocol to one leg of 24 rats. Fiber counts and sizes are analyzed on control soleus muscles and injured (CTD) soleus muscles using the image analysis program, OPTIMAS. Immunohistochemical markers are now in use for measuring the three major components of muscle basal lamina: laminin, heparan sulfate proteoglycan, and collagen IV on sectioned muscles. The use of tenascin as a marker for regeneration is under development and will be useful

in delineating regenerative processes from degenerative ones.

The extracellular matrix outside that considered the basal lamina appears to proliferate following repeated injury (CTD). 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 under 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. The implication is that the muscle would have a greater stiffness.

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*. Stiffness and isometric strength will 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. Stiffness will be measured by slowly moving the foot through small increments of muscle stretch stopping to record force and creep. Muscle weakness will be measured by stimulating the nerve to the soleus muscle and measuring the force output (isometric muscle action) while the foot is held at 90 degrees of ankle extension. Material fatigue will be determined by measuring the decrement of force during repeated strain overloads. Preliminary studies have been undertaken to validate the feasibility of all the tests except the stiffness measurements which will require the servomotor control. The control programs are nearing completion and should be in operation within a couple of months.

Significant Findings

Muscle and non-contractile tissue proliferated following repeated strain injury. The size of the myofibers was smaller but there was an increase in fiber number. When analyzed more carefully, two populations of fibers were present: (1) one population of very small fibers (regenerating) and (2) one population of atrophic adult myofibers – both contained within a slightly larger muscle. This unique combination of hyperplasia and atrophy has never been reported before and may have profound physiological consequences.

Part of the increase in muscle size 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 that the muscle would have a greater stiffness.

The physiological outcome of such dramatic muscle changes can be tested on a custom-built dynamometer which has provided quantitative evidence for an increased material fatigue following inactivity of hind-limb muscles. The ability to measure the ability of CTD muscle to withstand strain overloads will be an exciting component of our continuing work.

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

None to date.

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

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

1. There are significant differences in trunk muscle activity during unexpected load application between:
 - (a) subjects with "lumbar instability" and normal controls and
 - (b) subjects with different load exposure histories [seated 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.

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

Methodology

Trunk muscle activity (via surface electromyography) and main and coupled mechanical driving point impedance (via brief vertical vibration exposures for mechanical response assessment) of the subjects will be recorded and used as the outcome

measures of the tests. 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 flexion load applied to the subject, performed before and after sustained exposure to the specific loading environments.

Significant Findings

None to date.

Quantitative Assessment of Carpal Tunnel Syndrome

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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 threshold and electrophysiological measures, all Group 1 subjects, regardless of treatment, will be invited to undergo repeat testing 7 months following entry into the study. The change in subjective symptomatology will be compared to

changes in vibration threshold and electrophysiological parameters.

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

Significant Findings

Objective 1. At this time, 115 subjects have been evaluated. Analyses were performed separately for the dominant and non-dominant hands. For the dominant hand, 21 subjects met the criteria for Group 1, 20 for Group 2, and 59 for Group 3. For the non-dominant hand, 16 subjects met the criteria for Group 1, 17 for Group 2, and 65 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 0.53 (SD=0.85) among Group 1 subjects ($p=0.01$). At a specificity of 80%, the sensitivity of this measure for detection of dominant hand carpal tunnel syndrome was 52%. 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 0.24 (SD=0.93) for Group 1 subjects ($p=0.08$). At a specificity of 80%, the sensitivity of this measure for detection of dominant hand carpal tunnel syndrome was 33%.

The 2-5DIF after the wrist flexion period for the non-dominant hand were 0.08 (SD=0.44) among Group 3 subjects, and 0.74 (SD=1.33) among Group 1 subjects ($p=0.03$). At a specificity of 80%, the sensitivity of this measure for detection of dominant hand carpal tunnel syndrome was 63%. The DELTA 2-5DIF was -0.05 (SD=0.37) for Group 3 subjects and 0.66 (SD=0.90) for Group 1 subjects ($p=0.007$). At a specificity of 80%, the sensitivity of this measure for detection of dominant hand carpal tunnel syndrome was 69%.

Objective 2. None to date.

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.

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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.

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.

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.

Psychophysical measures of localized fatigue and discomfort are being correlated with posture and force spectral components. These measures are being investigated for use in designing digital filters for frequency-weighted physical stress measurements in order to control strain associated with repetitive tasks.

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.

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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 ICP and hand maneuvers are consistent between subjects, (2) develop a mathematical model that will predict ICP based on hand maneuvers, and (3) determine whether there is a dose-response relationship between two currently accepted risk factors (repetition and wrist angle) and ICP in subjects performing simulated work tasks.

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

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 100 cases and 100 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 receive electrodiagnostic testing (distal sensory and motor latencies of the median nerve), clinical exams (Phalen's test, Tinel's test, and measurements of wrist size and dimensions), and a personal interview. The case-control interview includes more extensive questions on CTS symptoms, medical history, and occupational work task information. Cases are selected on the basis of their reporting of CTS symptoms in the cross-sectional survey; controls will be selected among those who do not report CTS symptoms. Controls are matched to cases by age, sex, and union.

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 research demonstrated the feasibility of using the GripMaster™ (GM) to measure the wrist motions and finger and hand forces in both the laboratory and factory environment. Specifically:

1. High correlations between GM grip forces and other techniques were observed when contact area was constant and sensors were new, and

2. Angle measurements were shown to be as accurate as current clinical techniques.

Operational parameters identified in the field provide additional requirements for further development of this technology.

In order for these findings to extend to a broader set of conditions and to allow the GM to become an ergonomic tool capable of quantifying CTD risk factors, the following additional investigations must be performed:

1. Improve force sensor robustness, range, and calibration techniques,
2. Improve angle sensor ranges, attachments, and calibration techniques, and
3. Develop statistical parameters and experimental techniques to make the results more immediately available and simpler to interpret.

Occupational Cancer Surveillance: New Approaches

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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 15,221 cancer patients were interviewed, including 6,107 with lung cancer, 2,259 with urinary bladder cancer, 3,145 with colon cancer, 1,367 with cancer of the rectum, 834 with cancer of the esophagus, 557 with stomach cancer, 410 with liver cancer, 270 with cutaneous melanoma, 143 with cancer of the salivary glands, and 107 with eye cancers. There were 3,366 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 will be 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 because it indicates that blacks must be included in occupational cancer epidemiology studies and that they must be evaluated separately from white men. Our analyses to date also indicate different risks in the same occupations and industries for men and women. The following summarizes significant results from analyses currently underway.

Preliminary analyses of occupation and industry groups at risk for stomach cancer revealed significantly elevated risks among women for: electrical occupations, assemblers, metal finishers, and foodworkers. Among assemblers, the Odds Ratio for black females was more than twice as large as that for white females. Women were at high risk for stomach cancer when employed in the aerospace industry. For men, elevated risk of stomach cancer was observed in several occupations: policemen, farming, driver sales, postal workers, assemblers, masons, military, and foodworkers. Several of these occupations revealed higher Odds Ratios among white males than among black males: farming, assemblers, military, and foodworkers. Males also had elevated risk of stomach cancer in several industries: agriculture, food manufacturing, computer manufacturing, automobile manufacturing, transportation, water utilities, oil and gas sales, alcoholic beverage sales, and military.

Preliminary analyses of the rare eye cancers revealed elevated risks among white females who were employed as laborers and as machine operators.

Elevated risk of esophageal cancers were observed among males working in agriculture, ferrous manufacturing industries, computer manufacturing, automobile manufacturing, ship manufacturing, and in instrument manufacturing. Risks were elevated for black males when employed as farmers, in driver sales, as laborers, as assemblers, as mechanics, as foundry and furnace workers and as dry cleaners. Black women employed as dry cleaners also were at elevated risk of esophageal cancer. White males employed as plumbers had elevated risk of cancer of the esophagus.

Preliminary analysis of cancers of the salivary gland, which have a higher incidence among women than among men, reveals some interesting occupational risks. Women working in two occupations had elevated risk of salivary gland cancers: assemblers and hairdressers. Men who worked as mechanics or machine repairers also were at high risk of cancers of the salivary gland. The industries that were elevated among women with salivary gland cancers supported the occupational risks observed: automobile manufacturing and beauty shops. Men working in oil and gas sales had an elevated risk of cancer of the salivary gland.

White men diagnosed with mesothelioma were most likely to have been employed as: electrical

workers, assemblers, roofers, plumbers, drivers, or military. Three industries also were elevated among white men diagnosed with mesothelioma: construction, utilities, and military.

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

Results of 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 purposes of this study are: (1) to identify and measure the various endogenous and exogenous risk factors and biological markers in order to differentiate individuals and subgroups according to their risk for bladder cancer; and (2) to evaluate the usefulness of various biological markers as

discriminators of risk and as intermediate endpoint markers.

Methodology

Members of a previously identified cohort of workers exposed to benzidine and unexposed controls are to be screened. Subjects are from five cities, Shanghai, Chongqing, Henan, Tianjin, and Jilin, in The People's Republic of China.

The objectives of the screening, relative to the following, are: (a) exogenous risk factors – characterize each study subject on the basis of personal medical history, family medical history, occupational exposure to benzidine or other bladder carcinogens, and cigarette smoking history; (b) endogenous risk factors determine whether the slow acetylator phenotype or urinary pH is predictive of risk for bladder cancer or for urinary cytologic abnormalities; and (c) biological markers – determine the prevalence of specific biological markers, i.e., morphologic changes identified by Papanicolaou cytology, and biochemical and morphologic changes identified by quantitative fluorescence image analysis (QFIA) cytology, and hematuria determined by a dipstick, and correlate these with each other and with exogenous and endogenous risk factors to determine which best discriminate individuals and subgroups at risk for bladder cancer. Because of advances in methods for marker analysis, the markers G-actin, p300/M344 tumor-related-antigen and DNA ploidy were determined in all the samples as a multiple marker profile. Each of these markers had been established as a strong marker for bladder cancer or bladder cancer risk in independent studies.

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

Significant Findings

Essentially all of the aims of the study were met fully. The screening was conducted in two phases, a pilot study in one of the cities to identify problems and test protocols, and the full screening, which amounted to 1686 exposed subjects and 388 controls. A total of 2084 exposed subjects and 439 controls were notified, so 81% and 88%, respectively, of each group participated. Complete questionnaire information, and blood and urine samples were collected from all the subjects, and shipped to the U.S. where most of the analyses have been completed. The data from two cities (Shanghai and Chongqing) have been subjected to preliminary

analysis. The only changes in the protocol were the substitution of markers as described above and alteration of the acetylator study forced by the inability to obtain two blood samples. The single blood samples are in storage for genotypic analysis.

Results of this study demonstrate that complex, field molecular epidemiologic studies can be developed and carried out, including the collection of cells for shipment to the U.S. for analysis. The results of the analysis showed that the benzidine exposed and unexposed populations could be distinguished from each other on the basis of their biomarker profiles and, moreover, an additional effect of smoking could be distinguished in the profiles as well. These results clearly establish that biomarker profiles can be used to develop a cohort risk map and to manage risk within such large cohorts by identifying subgroups at high risk.

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Case Control Study of Cancer in Synthetic Rubber Workers

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Program Area: *Occupational Cancers*

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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 will emphasize human effects from exposure to butadiene based on industrial monitoring measures to determine risk by dose.

Objectives

The goals of this research are to examine the risk of mortality from 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

Although the following results are preliminary, the investigators believe them to be accurate reflections of the data.

During hospital record review, soft tissue sarcomas, especially in the gastrointestinal tract, have been identified. Angiosarcoma and fibrosarcomas occur among these records at a frequency much higher than expected based on SEER rates.

Analyses using hospital diagnoses of lympho-hematopoietic cancers did not markedly change the observations from those made using death certificate reports. The association between butadiene and leukemia remains. For acute leukemia there is no apparent confounding by styrene.

Case-control analyses of gastro-intestinal cancers showed that the median score for butadiene is higher for cases than for controls for all sites combined and for esophageal, stomach, and colorectal cancer, but not for pancreatic cancer. Styrene scores are higher

for cases than for controls for all sites combined and for stomach and colorectal cancer, but not for esophageal or pancreatic cancer. Exact analysis of the case control sets matched for duration worked have compared cases and controls above and below the median to subjects With no exposure. Although some of the odds ratios are high for butadiene and styrene associated with esophageal cancer and there is a suggestion for increasing odds ratios with increasing butadiene exposure for colorectal cancer, the findings are not statistically significant.

The original study design used duration matched controls. Odds ratios for leukemia associated with butadiene and styrene were calculated using a new set of controls which were not matched for duration of employment. The new odds ratios were only slightly lower than those in analyses of duration-worked matches, but the p values were higher. In order to test whether this difference was related to the removal of the matching variable or to the specific set of controls chosen, a variable for length of employment was added. This increased the odds ratios for butadiene and reduced variance. Although these observations will need to be tested in larger populations of cancers, it does appear that controlling for duration worked improves evaluation of risk by removing the differences in opportunity for exposure in cases and controls.

To date exposures to both styrene and butadiene have been assigned to the case and control jobs based upon an expert ranking scheme. During this study period, records of actual exposure measurements taken in the past have been collected from both plant and NIOSH measurements. Since there is not a direct correlation between names of measured sites and job titles, it has been challenging to determine the best way to relate the measurements to the job histories used for lifetime exposure estimates in the case-control studies.

Mortality for long-term workers was available at the start of this working period. However, data from one plant had many missing birth dates causing these workers to be excluded from analysis. An algorithm was constructed to estimate the missing birth dates based on hire year and hire age. Data from another plant was missing race for quite a few of its workers. In the original analysis, these were included with the analysis of whites even though it was recognized that deaths among blacks (with race verified by death certificate) would be included in the analysis of blacks while person-years for living blacks whose race was unknown to us were included in the analysis of whites. Since it was known that many of the workers in one plant were black, it was desirable to account for these missing values. An algorithm for imputing race was developed based on records of workers from that plant who had race. Results of the mortality reanalysis of long-term workers showed the

expected increase in SMRs among whites (since a proportion of people were removed from the denominator when race was imputed) and decrease among blacks (since the black denominator was increased).

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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.

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- β , 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.

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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 ³²P-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 will be examined by isolating mouse white blood cells and incubating them with carcinogen for 12 to 24 hours under standard cell culture conditions. The cells will be harvested, DNA prepared, and adducts analyzed by ³²P-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 acetylase status. Studies of these variables have indicated that acetylase 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. Further, 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.

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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

We propose 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 the genotoxic effects of butadiene exposure.

Methodology

Butadiene workers involved in a monomer and polymer production will be studied. Exposure will be assessed primarily by questionnaire and workplace walk-throughs. Butadiene-exposed workers will contribute a blood sample and chromosomal endpoints analyzed. The individual sensitivity to the cytogenetic effects of diepoxybutane will be assessed. Analysis will determine if individual cytogenetic sensitivity to butadiene predicts the baseline level of chromosomal damage induced by butadiene exposure. In this way, susceptibility to the chromosomal effects of butadiene may be predicted by 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 weighted average personal sampling as well as urine collection and metabolite determination. Significant data has been collected by questionnaire and blood has also been collected. The study is currently in the hemeolytic phase and consequently, there are no significant findings that can be reported to date. 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 somatic 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.

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Activation of H-Ras Oncogene by N-Heterocyclic Aromatics

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Importance to Occupational Safety and Health

Polycyclic and N-heterocyclic aromatic hydrocarbons are ubiquitous pollutants being released into the environment from numerous sources such as coal tar, coke oven effluents, automobile exhaust, and cigarette smoke. Many of these compounds are

known to be mutagenic and/or carcinogenic, but little is known about the mechanisms involved. This study is designed to investigate the ability of two N-heterocyclics, dibenz(a, j)acridine (DBA), and dibenzo(c,g)carbazole (DBC) to activate the H-ras oncogene in mouse skin carcinogenesis. The activation of this oncogene has been implicated as playing a role in the etiology of several experimental as well as human tumor types.

Objectives

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

Methodology

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

Significant Findings

During the first year of the funding of this grant, the research focused on the NIH3T3 transfection assay. Tumor DNA was screened for its ability to transform the mouse fibroblast cell line resulting in the formation of foci. Positive results were obtained for transfections performed with DNA isolated from tumors induced by DMBA and DBA, but results from DBC samples could not be analyzed due to bacterial contamination. This technique is not currently being used. Initial work also involved looking at the electrophoretic mobility of the p21 protein encoded by the H-ras gene, as this can be used as an indicator of an amino acid substitution resulting from a DNA mutation. The preliminary results showed that there was a stronger ras signal seen in tumor samples than those from control mouse skins, and there was also

an indication that p21 from DBA tumors migrated faster than control p21, suggesting a mutation in codon 61. RFLP analysis of codon 61 showed an A/T transition in DMBA tumor samples, but results were inconclusive for DBA. These techniques are no longer being pursued.

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

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 aromatic amines e.g., 4-aminobiphenyl (4ABP), can cause tumors at the site (for the former) or at distant organs (as in the case of aromatic amine-caused bladder 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 frequencies) for two 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 micronuclei measurements in the workplace.

Objectives

The kinetics of DNA adduct levels (^{32}P post labeling assay) and micronuclei frequencies (cytochalasin-B blocking method) will be determined in mouse skin and liver for BaP and 4ABP respectively. The ability of both compounds (BaP and 4ABP) to cause chromosome damage in mouse skin and liver (as measured by micronuclei frequencies) will then be determined. Dose-response relationships will be established between carcinogen-DNA adducts and cytogenetic damage as measured by micronuclei frequencies. Finally, the mechanisms of clastogenicity will be evaluated by using centromere-specific antibodies for micronuclei formation in mouse skin and liver.

Methodology

The study has been divided into two main parts:

1. Kinetics Study – This will allow for observation of repair and will determine the times of maximum DNA binding and maximum micronuclei expression.
2. Multiple Dosing Study – This study will test whether chronic exposure to carcinogens will alter the relationship between DNA adducts and micronuclei frequencies.

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 4×10^6 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 Post labeling 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

1. Conditions have been established for the isolation, growth and maintenance of keratinocytes in

collagen coated microscope slides and petri dishes. Briefly, the skins from treated and control animals are excised, fat scraped away from the dermis, cut into square pieces and floated on a 0.25% trypsin solution for 2 hours. The epidermis is scraped from the dermis, epidermal fragments gently stirred at room temperature, resultant cell suspension filtered through a 70 μ M nylon mesh, centrifuged at 1500 rpm for 10 minutes, cell pellet taken up in medium and plated after obtaining a cell count and determining viability.

2. 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 post labeling.
3. Experiments were performed to optimize the conditions for obtaining maximal numbers of binucleate cells [Micronuclei are scored in 1000 cytokinesis-blocked binucleate cells]. Cells were grown for two days and cytokinesis was blocked (Cytochalasin-B [Cyto-B; 3 μ g/slide]). The slides were harvested 1 and 2 days respectively after the addition of the drug. The proportion of binucleate cells were maximal 2 days after the cells were cultured in the presence of Cyto-B [4.65% after a day and 34.2% after 2 days]. On the other hand, the majority of cells were uninucleate if Cyto-B was added a day after the keratinocytes were isolated and the slides harvested two days later, indicating that the cells do not divide during the first 24 hours of the isolation.
4. Conditions have been optimized for performing the micronucleus assay. The number of micronuclei (MN) in acetone treated controls were 20 MN/1000 binucleate cells scored.
5. The number of micronuclei in mice skin painted with 50 nmol/mouse [12.5 μ g of BaP] were 15 MN/1000 binucleate cells scored. This number is very close to the control value. This finding seems to indicate that a higher dose of BaP will be required to produce a significant increase in chromosomal breaks, as reflected by an increase in micronuclei, over acetone treated controls.

Cocarcinogenic Particulates in Coculture System

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Importance to Occupational Safety and Health

The respiratory tract is the most common route for entry of toxic materials from modern urban and occupational environments. 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 those particles, workers are also frequently exposed to polycyclic aromatic hydrocarbons (PAH). Benzo(a)pyrene (BaP), a well characterized and ubiquitous PAH, has been shown resistant to photodegradation under ambient conditions when adsorbed on particles. Therefore particles can serve as carriers for transportation of BaP to the lung as the parent compound via cellular phagocytosis. 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 mechanism of particle-mediated cocarcinogenicity. Male Syrian Golden hamsters (6-8 wks old) are used in this study based upon (1) low spontaneous lung cancer rate; (2) higher resistant to pulmonary infection and inflammation; (3) resemblance to humans in terms of histogenesis and pathogenesis. Primary alveolar macrophages (AM) and tracheal epithelial cells 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 overall feature of this project is to study the effect of particle upon the alteration of BaP metabolism and DNA binding. The profiles 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 the potentiation of pulmonary tumorigenicity. The proposed hypothesis is that cocarcinogenicity of particles with BaP is due to the enhancement of BaP metabolism in AM and potentiation the binding of BaP metabolism 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 the 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 will be used to measure the basal metabolic activity of AM. Ethyl acetate extraction and HPLC analysis will be conducted to determine the pattern and amount of BaP metabolites in the cells. ^{32}P -postlabelling will be performed to measure and identify DNA adducts in the cells.

Significant Findings

Several preliminary studies have been accomplished, including characterization of particles, culture condition of AM and tracheal epithelial cells, dose-response of particles to AM and the feasibility of coculture membrane. About 90% of ferric oxide (Fe_2O_3) is less than 5 μm , whereas 99% of aluminum oxide (Al_2O_3) is less than 5 μm . The count medium diameter of each particle is 1.28 μm for Fe_2O_3 and 0.36 μm for Al_2O_3 . The surface area (m^2/g) for Fe_2O_3 and Al_2O_3 is 6.9 and 149, respectively.

The optimal culture condition for the growth of AM and epithelial cells is at pH 7.2 in RPMI-1640 medium containing 2 mg/ml BSA and 0.1% gentamicin up to 48 hr. 1×10^6 AM have been plated in the above stated medium (2.5 ml/plate, 35 mm plastic dish) with various treatments, including BaP alone, particles ($\text{Fe}_2\text{O}_3/\text{Al}_2\text{O}_3$), or BaP-coated particles. The viability of AM were recorded at two time points (24 and 48 hr) and measured by

erythrosin B dye exclusion assay. Both Fe_2O_3 and Al_2O_3 have been shown to be noncytotoxic at 0.5 mg/plate. BaP has been shown to be noncytotoxic at 5 μg /plate. At the level of 5 μg BaP-coated 0.5 mg particles/plate, Fe_2O_3 , Al_2O_3 and BaP particles have been shown to be noncytotoxic.

With regard to the feasibility of coculturing AM with epithelial cells, AM were treated with BaP and plated on minipore insert membrane, 0.4 μm inside 35 mm culture dish. After 24 hr, the membrane were removed and the medium was collected. The medium was extracted with ethyl acetate and analyzed with HPLC. The results have indicated that BaP parent compound and its metabolites can pass through this coculture membrane.

Several preliminary studies have been accomplished, including characterization of particles, culture condition of AM and tracheal epithelial cells, dose-response of particles to AM and the feasibility of coculture membrane. About 90% of ferric oxide (Fe_2O_3) is less than 5 μm , whereas 99% of aluminum oxide (Al_2O_3) is less than 5 μm . The count medium diameter of each particle is 1.28 μm for Fe_2O_3 and 0.36 μm for Al_2O_3 . The surface area (m^2/g) for Fe_2O_3 and Al_2O_3 is 6.9 and 149, respectively.

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 quantitatively 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.

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Reduction of Occupational Injury Deaths in Rural Colorado

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Importance to Occupational Safety and Health

Half of the occupational injuries in Colorado that result in death occur in rural areas where only 20% of the workforce resides. Thus, rural occupational injury deaths constitute a major public health problem in Colorado, and if this pattern holds in other states with rural areas, it represents a public health problem nationally. Major risk factors contributing to the rural/urban difference in occupational injury mortality will be identified in this study.

Objectives

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

Methodology

Occupational injury deaths are ascertained primarily by linkage of workers' compensation claims (WC), OSHA case reports, and death certificates (DC). Additionally, motor vehicle traffic accident reports are linked for occupational traffic deaths.

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

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

Significant Findings

The temporal trend in occupational injury deaths for the 1982-87 period demonstrated a steady decline in deaths and this trend has continued through 1990. During the five-year period examining rural/urban differences in trauma care effectiveness, the number of deaths declined from 117 in 1986 to 73 in 1990 for a total of 467 deaths. The five-fold rural/urban

ratio persisted as did the six-fold greater rate among employees of firms with fewer than 500 employees.

Circumstances of Injury have been studied for eighty cases of civilian non-transportational unintentional injury deaths and have had active case investigations between April 1989 and June 1991. The project industrial hygienist has adapted the classification system of the Loss Control Institute to assign primary, indirect, and basic causes to these deaths. An average of 2.6 hazardous practices and 3.6 hazardous conditions were identified for each case. The most striking finding is that in over 90% of the cases both hazardous practices and conditions were identified. Rural/urban differences included significantly greater number of hazardous conditions in the rural area. Two major categories contributing to these differences were workplace environmental hazards and natural hazards. Four categories were greater among deaths in firms with fewer than eleven employees: poor judgment; use of inherently hazardous materials, equipment, methods/procedures; inadequate assessment of loss exposure; and, improper use of equipment.

Trauma Care Effectiveness (TCE) was determined by geographic area for fatal and severe nonfatal occupational injuries. Overall statewide TCE was 71%. TCE was comparable in Denver Metro (72%) and the Rural region (68%). However, when the insufficient information cases were considered salvageable in both regions, the TCE in the Rural region was significantly lower at 54% ($p < .05$). When the TCE calculation is restricted to those cases that reach the hospital, no rural/urban differences in TCE are observed even when the insufficient information cases are factored in. EMS effectiveness was substantially lower in the Rural region (40%) when compared with Denver Metro (61%) and may be due to largely unalterable factors such as terrain and long distances. It is concluded that TCE does not explain more than a small portion of the rural/urban differences in mortality. The major reason for the rural/urban mortality difference is the increased rate of serious injuries in the rural region. Over the five-year period, the rate of serious injuries in the rural region is estimated to be 13.8 per 100,000 compared to 5.1 in the Denver Metro region. The following recommendation are made for intervention efforts focusing on pre-event and event factors:

- (1) Institutionalize population-based occupational injury surveillance.
- (2) Establish a statewide Occupational Injury and Fatality Intervention Program.
- (3) Communicate the Active Case Investigation findings to the OSHA Consultation Program and the Colorado Worker's Compensation Authority.
- (4) Study whether preventability factors identified for fatal injuries apply also to serious nonfatal injuries.

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The Health Hazards of Child Labor

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Importance to Occupational Safety and Health

The principal findings of this study were:

1. The employment of children is widespread in the United States today, and this employment frequently takes place under hazardous and exploitative conditions. More than 4 million American children under the age of 18 are gainfully employed. Many of these children are employed under extraordinarily unsafe conditions, for example, in sweatshops.

Violations of Federal Child Labor Law have increased four-fold over the past decade.

2. The employment of children, particularly employment that occurs under unsafe and exploitative conditions, results frequently in injury and disability. We found that each year in New York State more than 1,200 children receive Workers' Compensation awards for injury incurred on the job. In epidemiologic studies, we defined the patterns for these injuries by occupation, industry, and body part affected.

Objectives

The principal objective of this study was to determine the extent, severity, and patterns of injury to working children in New York State.

Methodology

The principal approach used in this study consisted of a descriptive epidemiologic analysis of data on occupational injuries to children in New York State. Data were obtained principally through the Workers' Compensation Board. The data were subjected to epidemiologic analysis in which rates of injury to working children were determined by age, sex, occupation, type of injury, industry, occupation, and calendar year. On the basis of this analysis, we defined the major patterns of childhood occupational injury in New York State.

Significant Findings

The two most significant findings of this study were noted above. In summary, we found that occupational injury is a major contributing factor to the current epidemic of childhood and adolescent injury that is currently occurring in the United States.

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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 workforce. 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 will be employed, in which cases will be 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 will be selected from employee lists provided by participating employers or from membership lists provided by participating union locals.

All subjects will be interviewed to obtain information on demographics, anthropometry, work

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

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

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

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

respirator use, weight of loads handled, and condition of the floor surface.

Significant Findings

None to date.

Probabilities of Job-Related Deaths and Disabilities

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Importance to Occupational Safety and Health

While the Bureau of Labor Statistics regularly publishes lists of industries according to nonfatal illness and injury rates, few lists of jobs are available that rank occupations or industries by mortality rates. This is unfortunate for two reasons. First, OSHA resources need to be targeted to not only high risk industries but high risk occupations as well. Second, the public would benefit from having greater information of job hazards just as they benefit from nutrition labels on packaged and canned food. Future laws may require that job hazards and mortality statistics be included on all job application forms. (Employers should inform prospective employees of job hazards, Occupational Hazards, Vol. 53 no. 1 (Jan 1991): 45-46).

Objectives

The proposed research will generate tables of job-related death rates within roughly 350 occupations and industries.

- (1) Death rates for men and women, 1979-1983, by 3-digit occupation
- (2) Death rates for men and women, 1979-1986 by 3-digit industry
- (3) Death rates women only, 1979-1986 by 3-digit occupation
- (4) Source and nature of injury or illness resulting in death

Tables 1 and 2 will also contain the source and nature of injuries or illnesses within each occupation or industry. Only the "top 3" sources and natures will be provided, however.

The proposed study will compare these rankings, sources, and natures with prior studies and will compare women with men.

Methodology

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

The proposed research will build on a prior study which used some of the early SDS data (*J Occup Med* 29:510, 1987). The prior study used only fatality data from 11 states during 1977 to 1980 to construct annual rates of job-related deaths within 347 occupations. Rates were calculated by taking the ratio of fatalities to estimated employment within each occupation for each state and each year. The proposed research will differ from the prior 1987 study by (1) considering industries; (2) considering the most recent years available; 1981, 1983, 1985; and (3) separating male from female job-related deaths and (4) analyzing causes of deaths within each occupation or industry.

Significant Findings

The 1980 SDS data tapes yielded information on 1,082 deaths. These deaths were from states which contributed 14.846 percent of total U.S. employment. The estimated number of total U.S. occupational deaths for 1980 would then be $1/.14846 \times 1,082 = 7,288$. This figure of 7,288 closely resembles the 7,000 estimate produced by the National Traumatic Occupational Fatality Study by NIOSH (Bell et. al. *JAMA*, vol. 263, no. 22, June 1990: 3047-3050).

The 1979-81 and 1983 SDS data tapes produced the following ranking of occupations for men and women together with their annual death rate per 100,000 and top cause of death: stone cutters, 351, silicosis; blasters, 123, silicosis; airplane pilots, 117, aircraft crash; motormen, 112, tractor accident; chainmen, 89, highway vehicle crash; lumberjack, 80,

tree fall; painter apprentice, 78, fall; miscellaneous labors, 67, highway vehicle crash; asbestos workers, 65, asbestosis; electric power linemen, 55, electric shock. The same years produced this ranking for women only: airplane pilots, 189; earth drillers, 179; crane workers, 53; geologists, 35; metal molders, 30; miners, 27; miscellaneous laborers, 23; engineer, n.e.c., 15; airline stewardesses, 13.

The 1979-91, 1983, 1985, 1986 SDS data produced the following ranking of industries for men and women together with their annual death rate per 100,000: logging, 191; taxicabs, 108; cut stone, 105; heavy construction, 105; sanitary services, 79; suburban transportation, 57; highway construction, 47; iron ore mining, 40; crushed stone, 37; trucking, 33; water well drilling, 32; fertilizers, 31; miscellaneous special trade contractors, 31; sawmills, 28; water supply, 27.

Causes of deaths in 1979-81 and 1983 and number of deaths were as follows: highway vehicle crashes, 901; person, injured, 255; bullets, 235; nonclassifiable, 221; minerals, 158; ground, 153; floor, 153; aircraft crashes, 121; fire and smoke, 97.

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 the United Kingdom and Israel 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 [via the measurement of postural sway and index of proximity to stability boundary (IPSB)]. 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. The current pool of industrial subjects represent a wide range of occupations such

as: radio operator, sales, fire fighter, dock/receiving, custodian, vehicle operator, plumber, health care, student, heating/air conditioning technician, clerical/secretary, store clerk, service, postal worker, laborer, day care worker and assembly line worker. These tests simulate conditions which occur in industrial/occupational environments. 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 newly designed 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.

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 14 subjects who have completed the testing protocol (providing data from 3136 postural tests) has been performed. Despite the small sample, 4 of the 5 conditions (workload, surface firmness, 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. The only experimental condition not demonstrating significance at this time is the surface condition (dry vs. oily). 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 type 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. Data from additional subjects are currently being collected and the final report will

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, 200 Hz, the amplitude is 0.200 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

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 three major tasks: (1) Knowledge acquisition, (2) Fault tree development, and (3) Expert system development.

During the knowledge acquisition process, we function as the knowledge engineer who communicate with the experts, gather information from literatures, and build the knowledge base. Our project is now at the knowledge acquisition stage. Weekly meetings with the experts are conducted in the first three months of the project, followed by monthly meetings throughout the first year, and continued with bi-monthly meetings till the end of the proposed research project. The knowledge engineer meets with his mentor/advisor on a daily basis in the first three months of the project and on a weekly basis thereafter. We perform three phases of knowledge acquisition: preliminary discussion, detailed discussion, and organization.

Expert knowledge will be represented by fault tree models. A fault tree is a graphic model that shows parallel and sequential causes or events contributing to a predetermined top undesired event. In SAFETY FIRST, we will predetermine CONSTRUCTION FALLS as our top events. From the top events, the sufficient and immediate causes are developed through the use of logic gates. Each cause is further developed to reach the basic causes contributing to the occurrence of the top event. Development of fault tree models include fault tree logic evaluation, fault tree modeling, and qualitative and quantitative analyses.

The development of the expert system will include knowledge base development and system validation. The fault tree models described earlier will be used as a knowledge representation in SAFETY FIRST. These models represent the path of knowledge an expert will take in reaching a conclusion. The knowledge acquired from experts and literature is organized in each path. A piece of knowledge exemplified earlier 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 an 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. Validation process performed by the knowledge engineer (the proposer) will check the knowledge base of SAFETY FIRST for its accuracy and efficiency. Validation process performed by the participating experts will maintain completeness, accuracy, and user-friendliness of SAFETY FIRST. Validation by non-participating experts will maintain all the above, including the objectiveness of the system.

Significant Findings

None to date.

The Effect of Localized Fatigue on Postural Stability

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Importance to Occupational Safety and Health

Slips and falls at work account for 14–23% of all lost-time work injuries, and a mortality rate of 4.6 deaths per year per 100,000 workers. Injuries from slips and falls are frequently serious, with an incidence rate rising in direct proportion to increasing age. Tiredness or fatigue has been cited as an important risk factor for slips and falls in the high risk construction and manufacturing industries, because the most common activities performed prior to falls from elevations are static postural efforts and manual materials handling. Although uncontrolled high energy expenditures during dynamic work may eventually lead to fatigue, static work activities can produce localized muscle fatigue and discomfort after short duration activities. Given the significant economic costs and chronic disability associated with falls, more emphasis must be given to identifying and controlling those factors responsible for falls in high risk industries. To date, there are no existing guidelines that consider the criteria of postural

stability during the evaluation and control of fatigue during static work and manual lifting.

Objectives

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

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

The specific objectives for year two of the project are:

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

Methodology

A total of 36 healthy males, aged 21-35 years, will be studied during each experiment. Males were chosen because of the stressful nature of the lifting task. Fatigue estimates of standing steadiness, heart rate, ratings of perceived exertion, and ratings of discomfort will be the dependent variables to be collected prior to and following each condition for all experiments. During Experiment One, subjects will be exposed to fatigue of six postural muscle groups at two levels of loading. The level of loading on each individual postural muscle group (plantar flexors, dorsiflexor, knee flexors, knee extensors, trunk/hip flexors, and trunk/hip extensors) will equal

30% or 70% of the muscle group's maximum static strength, maintained as long as possible by the subject. During Experiment Two, subjects will be exposed to four doses of fatigue in three different work postures. The doses of fatigue will be 25%, 50%, 75%, and 100% of the maximum holding time for manipulating small pegs in the stooped or crouched postures. The highest maximum holding time for the stooped or crouched posture will be used to set the holding times for the comparison of erect standing posture. During Experiment Three, subjects will be exposed to two frequencies of lifting (2 & 6 lifts/minute) the NIOSH Action Limit in the same three work postures used for Experiment Two. The basic design for each of the three experiments will be a fractional factorial Latin-square design, to allow assessment and balancing of any systematic or additive effects associated with the order of testing, related practice, fatigue, transfer of training, etc.

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

Significant Findings

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

Analysis of Seafood Processing Injuries/Illnesses

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Grant Number: *1 R03 OH02656-01*
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Importance to Occupational Safety and Health

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

Objectives

The objectives of the study are:

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

Methodology

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

Significant Findings

Significant findings to date include the following:

1. 2,707 workers' compensation claims were filed by workers over the three year period 1985 – 1987. During that period, 85% of all claims involved a work-related injury.
2. Seventy-five percent (74.8%) of all work-related injuries/illnesses sustained by seafood processing workers occurred within the first three months of employment.
3. Seventy-five percent (75%) of all claims were filed by workers employed as packing and filling machine operators and miscellaneous food handlers. These two occupations account for approximately 62% of food industry employment.
4. Men accounted for approximately 67% of the seafood processing industry's workforce but filed almost 80% of all injury/illness claims.
5. Women filed proportionately more illness claims than men. The percentage of illness claims filed by women was approximately twice that of men.

Men filed 15% more injury claims than did women.

6. Sprains and strains of the back and trunk were the most frequently occurring category of injury claims.
7. The nature of the injuries by frequency involved sprains and strains (35%), contusions and bruises (17%), cuts and lacerations (12%), and fractures (8%). The body parts most frequently involved in work-related injuries were wrists, hands and fingers (26%) and trunks/back (30%).
8. Cumulative trauma disorders (CTDs) of the hand/finger and wrist were the most frequently occurring category of illness claims. Over 50% of all illness claims involving inflammation or irritation of the joints, tendons, and muscles were confined to the wrists and hands (packaging and filling machine operators: 52.5% and miscellaneous hand workers: 52.85%). Among all claims, those involving the wrists and hands accounted for 1.5% of the work-related trauma among packaging and filling machine operators and 2.8% of the injuries among the miscellaneous hand workers. Wrist and hand nerve trauma accounted for only 0.3% of the work-related trauma among workers in all other occupational groupings.

Publications

Catlin M, Trapp P: A Description of Work-Related Injuries in the Seafood Processing Industry in Alaska, 1985 – 1987. Proc of the American Public Health Association 119th Annual Meeting, Atlanta, GA, November 10 – 14, 1991

Incidence of Work-Related Injury

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Importance to Occupational Safety and Health

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

Objectives

The principal aim of the project is to make estimates of the frequency of occurrence of workplace injuries that result in either an emergency room (ER) visit, a lost-time claim coded by the Ohio Industrial Commission, or both, for Athens County, Ohio during the years 1982-86.

A secondary aim is to compare this incidence estimate to the expected number obtained by applying national BLS industry-specific incidence rates to the number of persons employed in Athens County by industry.

Methodology

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

Significant Findings

The NEISS and worker's compensation (WC) datasets from 1982-86 were reviewed and matches identified by application of an algorithm developed to look at social security number, date of injury, age, sex, and type and location of injury. The total of ER visits plus workers compensation claims is approximately 1,000 per year. This number was

derived after accounting for duplicate records appearing in both datasets, after correcting for the number of occupational injuries seen in the ER but not entered into the NEISS dataset, and after extrapolating from a one-sixth sample the number of ER visits to a secondary hospital in the county. Only 12.4% of the injuries appeared as matches between the NEISS and WC datasets. NEISS data detected an estimated 81.2% of the total injuries, while WC data detected 25.5%.

Three new datasets were created using the information comparing the NEISS and worker's compensation data. These were: (1) matched records, appearing in both NEISS and WC; (2) NEISS only, consisting of all NEISS records minus those matched to WC records; and (3) WC only, consisting of all WC records minus those matched to NEISS records. The distribution of injuries by age, sex, diagnosis, body part, and accident type were then calculated for each dataset, including the entire NEISS and WC datasets, and compared. The NEISS records showed a greater incidence of the accident types "struck against" and "struck by"; of injuries to the hands, fingers, face and mouth, and eyes; and of the diagnoses contusion/crushing/bruise/abrasion, foreign substance, and laceration/avulsion/puncture. The WC records showed a greater incidence of the accident types "fall on same level", "bodily reaction", and "overexertion"; of injuries to the lower trunk, unspecified back or vertebrae, and involvement of more than 25% of the body; and of the diagnoses dislocation, fracture, strain/sprain, and miscellaneous.

The county workforce was estimated with data from various sources, including the Ohio Bureau of Employment Services (BES) and Census Bureau County Business Patterns (CBP), and verified or amended by personal contact with more than fifty major employers in the area. Significantly, the number of miners in the service area of the county hospitals was greatly underestimated, and a large number of part-time workers at a local university were not included, in the published statistics. Published injury rates from the Bureau of Labor Statistics (BLS) were applied to the published statistics and to the amended estimate of the workforce. The predicted number of injuries is less than the actual number in both calculations, but closer with the amended estimate.

Based on the examination of the NEISS and WC datasets, we conclude that neither dataset alone gives a complete nor an accurate picture of occupational injuries in Athens County. The two may provide a more complete representation of occupational injuries when examined together. Using the NEISS and worker's compensation datasets in combination results in a total number of injuries higher than that predicted by national norms.

Publications

Fingar AR, Hopkins RS, Nelson M: Work-related Injuries in Athens County 1982 to 1986: A Comparison of Emergency Department and Worker's Compensation Data. J Occupational Medicine 34(8):779-787, 1992

Hopkins RS, Nelson M, Lalonde C: The Incidence of Work-related Injury: Comparison of Emergency Department and Worker's Compensation Data. Am J Epidemiol 132:762, 1990 (Abstract)

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. It therefore seems plausible that race and lead may interact to enhance the blood pressure response to endogenous catecholamines. Across all age groups, black Americans have higher blood lead concentrations than do whites, and the contribution of occupational and environmental lead exposure to the high prevalence of hypertension among blacks may be substantial.

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 bone lead concentration may enhance investigation of dose-response relationships in lead-associated disorders.

Objectives

The research objective is 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. Targeting enrollment to specific subject populations will enable the impact of race and cumulative lead exposure to be explored.

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 ¹⁰⁹Cd 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. 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.

Significant Findings

Normative data on K x-ray fluorescence measurement of bone lead concentration have been collected on 100 subjects, age 11 to 78. A newly

devised occupational history algorithm, which yields an estimate of lifetime occupational and avocational lead exposure graded by probability and intensity of exposure, indicated that the studied cohort had insignificant 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 $\mu\text{g/dl}$), 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. This model 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.

Two black men have completed the norepinephrine infusion protocol. The first subject was a 52-year old demolition worker with an initial blood lead concentration of 17.3 $\mu\text{g/dl}$ and baseline diastolic blood pressure between 95 to 105 mmHg; the second subject was a 57 year old scrap metal worker with an initial blood lead concentration of 56.6 and baseline diastolic blood pressure between 90 to 95 mmHg. The norepinephrine infusion protocol produced a linear dose-response in blood pressure. Blood lead measurements, plasma norepinephrine assays for calculation of concentration-pressor response relationships, and twenty-four hour measurements of urinary lead, electrolytes and creatinine have been collected. Up through the first six subjects, investigators will remain blinded to the order of the interventions.

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Occupational Risks of Pesticide Exposure for Females

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Importance to Occupational Safety and Health

The increase in the number of females finding their way into the everyday workplace has captured the attention of researchers. There is an urgent need to evaluate the exposure risk of toxic chemicals on the female reproductive system. The fact that women can no longer be discriminated against when applying for a position in which exposure to a hazardous agent is a reality insures that more women will face increased risk of toxic exposure. Thus, it is imperative that we evaluate toxic exposure to women both prior to and during pregnancy.

Objectives

This study will provide a comprehensive assessment of the toxic effects of the estrogenic pesticide methoxychlor on specific segments of the reproductive tract: the uterus and oviduct. 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 us to develop 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) will be exposed to specific doses of methoxychlor for five consecutive days/week for four weeks. Animals will be sacrificed either immediately following exposure

or at six months following exposure. In the second part of this study pregnant mice will be exposed to methoxychlor prior to or following implantation. Biological markers to be utilized to evaluate cellular toxicity of methoxychlor include histochemical evaluation of important metabolically active enzymes and the characterization of specific carbohydrate components of the mouse uterus and oviduct through the use of fluorescent-labelled lectin probes. In addition morphometric measurements on specific cell groups of the uterus and oviduct and chromatographic assays for incorporation of methoxychlor will be conducted. Additionally, an assessment of the fecundity and fertility of both groups of mice following exposure will be conducted.

Significant Findings

Non-Pregnant Females

Mice exposed for four weeks to any of the doses of methoxychlor (1.25, 2.5, 5.0, or 10.0 mg) increased in weight comparable to that seen in non-treated and the sesame oil vehicle-treated controls. Thus, there was no growth retardation induced by the pesticide. There was a dose-related response to methoxychlor with respect to the onset of persistent vaginal estrus. The majority of methoxychlor-treated animals had reached this condition by the end of the second week of treatment with the exception of the 1.25 mg. methoxychlor treated group.

Preliminary data acquired from a morphometric evaluation of the height of the endometrial lining cells of the uterus revealed a dose related response following a four week exposure to methoxychlor. The higher the dose of methoxychlor the larger the height of the endometrial cells. This is interpreted to be an estrogenic response resulting from the estrogenicity of methoxychlor. This effect on the uterine lining might certainly impact on future pregnancy.

Pregnant Females

Exposure of pregnant females on Day 6 of pregnancy to either estradiol-17 β , or 2.5, 5.0, 6.0 or 7.5 mg of methoxychlor appeared to have no effect on either vitality of embryos or uterine morphology one day later. This perfect viability continued in the sesame oil control group following two and three days of exposure.

The estradiol-17 β control group showed a continuing decrease in viability beginning on Day 8 following exposure on Days 6 and 7. The 2.5 mg methoxychlor dose showed little or no deleterious effects on the developing embryos. However, with the higher doses there was a decrease in survivability.

With as little as two days exposure (Days 6 and 7) at 5.0, 6.0 or 7.5 mg methoxychlor there was less than 50% litter survival. Following an additional day of exposure, the survival rate was below 35%. Indicative of the loss of viability, animals receiving doses of methoxychlor above 5.0 mg showed a bloody vaginal discharge signifying uterine hemorrhaging by the eighth day of gestation.

The histological appearance of the uterus in those pregnant females receiving the higher doses of methoxychlor was initially an increase in the number of white blood cells appearing in the uterine capillaries which is an initial sign of inflammation. This is followed by edema and necrosis at the implantation site. Finally, there is a sloughing of the uterine tissue containing the implanted embryo with subsequent expulsion of this mass as a bloody vaginal discharge. Thus, methoxychlor at the time of pregnancy administered here does not support early embryonic development. What effect it might have on future pregnancies is not known.

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Occupational Exposures and Birth Defects

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Importance to Occupational Safety and Health

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

Objectives

The objective of this project was to evaluate the utility of the NIOSH JEM as a tool for investigating potential associations between workplace exposures and birth defects and, assuming this tool proved useful, to establish a large-scale, epidemiologic data resource to facilitate study of such associations. Information was drawn from the BDS, which had data on over 11,000 infants with a wide variety of birth defects. For each malformed infant, the BDS

data base contains information on maternal and paternal occupation and industry. The parents' specific occupational exposures were derived by applying the JEM to these data. By combining data from a large, well established birth defects surveillance program, we expected to develop a valuable resource for generating and testing hypotheses regarding the risks and safety of occupational exposures.

Methodology

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

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

subsequent testing and generation of hypotheses regarding occupational exposures and birth defects.

In the final phase of the project, we explored selected aspects of the data in some detail. Based on phase II results, we selected a specific hypothesis for investigation (benzene exposure in relation to kidney malformations), and in the course of that analysis we attempted to verify the JEM exposure assignments and probabilities. This process included an analysis of the hypothesis, validation of the relevant code translations, validation of exposure attributions by the JEM, and examination of exposure probabilities in the JEM.

Significant Findings

We found that neither the absolute attribution of exposure nor the assessment of exposure probability by the JEM provided a credible measure of exposure. Ignoring the levels of probability associated with each exposure and industry-occupation pairing would, under the best of circumstances, result in a high degree of misclassification. To select a level of probability above which exposure is considered to be plausible assumes that the JEM-assigned probabilities provide an accurate measure of the likelihood of exposure. Based on the assessments of occupational and industrial health consultants, this does not appear to be the case. Because of the nature of our analysis, it is not clear whether this is due to limitations of the JEM or to problems inherent in attempting to infer occupational exposures from job titles. Whichever the case, we must conclude that the NIOSH JEM cannot be usefully applied to the BDS data base to assess risks of occupational exposures in relation to birth defects.

Menstrual Function and Physical and Mental Job Stress

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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 will investigate menstrual function in women workers and study effects of physical and mental job stress, and stress-related behaviors like caffeine consumption on cycle characteristics and ovarian hormone patterns. Stress is a pervasive occupational exposure and one that potentially can be prevented or reduced. It has been implicated in menstrual disorders and has also been cited as a possible alternative explanation for adverse pregnancy outcomes among workers exposed to other agents (e.g., VDTs). Job stress may be a particular problem for women whose added responsibility for the so-called "second shift" does not readily allow for recovery from 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).

The primary specific aims are:

1. To develop a profile of ovarian and pituitary hormone levels (LH, E₁G and PdG) for each of three nonconceptive menstrual cycles from 100 subjects, based on daily samples of their first urine void.
2. To estimate the frequency of cycles that are short; highly variable; anovulatory (no detectable LH surge or shift in estrogen to progesterone ratio); and likely to have a luteal phase defect (progesterone level <4ug/ml or luteal phase length <8 days).
3. To investigate the associations between these markers of menstrual function and exposure to self-reported physical and psychological job stress. In addition to self-reported data, salivary samples will be used to measure cortisol, one of the stress hormones. Stress-related behaviors like caffeine consumption will also be studied as will exposure to antineoplastic medications. Factors such as subject's age, body mass, and leisure-time exercise will be considered to be potentially confounding and will be addressed as

needed using multivariate statistical techniques. Additional analyses will compare absolute levels and rates of change in estrogen and progesterone metabolites in relation to exposure.

4. Finally, using urine hormone data as the gold standard, we plan to examine the validity of two less demanding tools for measuring menstrual function in future field studies — basal body temperature records and menstrual diaries.

Methodology

We have enrolled over 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; high caffeine intake and willingness to comply with a demanding regimen also seemed likely based on a feasibility study conducted prior to the start of the study. To maximize the range of job stress levels, subjects were recruited from areas of the hospital judged to be "high" and "low" stress. High and low stress units at MSKCC were identified on the basis of archival material and discussions with administrators.

Subjects are 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 (E₁G), 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. Given the substantial differences in training and work conditions for nurses in the U.S. and Italy, this could yield potentially interesting comparative data.

Significant Findings

Data collection is expected to be complete by January of 1993. To assess the success of our recruitment strategy in providing a range of job stress levels, we examined preliminary data from 30 subjects, 17 from units identified as high stress and 13 from units identified as low stress. A comparison of means (with higher scores indicating higher job stress) was made for several scales:

	"Low stress"	"High stress"	p-value (2-tailed)
Workload and Variance in Workload	24.72 (± 6.46)	29.54 (± 5.25)	.015
Role conflict and ambiguity	25.64 (± 7.16)	27.94 (± 5.33)	.001

In each case, the mean score for subjects from high stress units is higher than for subjects from low stress units. The range in scores is quite wide and there is overlap in the ranges for subjects from high and low stress units (ranges are: low stress 8–40 and 13–43; high stress 13–40 and 13–46 for workload and variance in workload and role conflict and ambiguity respectively.) Thus, while work location was useful as a sampling strategy, the statistical analyses must be based on individual-level assessments.

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Semen as a Biomarker of Effect Among Lead Exposed Men

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Importance to Occupational Safety and Health

This study will provide useful 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 will be a cross-sectional survey of approximately 100 men with known occupational exposure to lead and approximately 100 unexposed referent subjects of similar age. Blood and urine samples will be obtained to determine lead exposure. Acute lead exposure will be determined by blood lead and δ -aminolevulinic acid levels, and chronic lead exposure by urinary coproporphyrin excretion profiles. Demographic data, occupational and reproductive history, and the presence of potential confounding variables, such as alcohol use and existing disease states, will be obtained by questionnaire. Semen quality will be determined by traditional semen quality assays (sperm count, morphology, and motility) and newly developed flow cytometric techniques (sperm chromatin structure assay (SCSA), mitochondrial function, and glutathione content).

The effects of acute lead exposure on semen quality parameters will be assessed by comparing the measures of semen quality between subjects with high, moderate, low, and unexposed lead exposure. The epidemiologic utility of urinary coproporphyrin profiles as biomarkers of lead induced damage will be determined by relating porphyrin excretion patterns to blood concentrations of lead and δ -aminolevulinic acid, and by comparing the measures of semen quality between subjects with high, moderate, and low levels of chronic lead exposure. Standardized fertility ratios will be calculated for the study subjects classified by acute and chronic lead exposures (none, low, moderate, high) to estimate the fertility of lead exposed workers.

Significant Findings

None to date.

Reproductive Health of Female Migrant Farm Workers

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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. The physically demanding and exerting tasks, as well as potential environmental contamination, climatic extremes, and unsanitary conditions in the field, may well increase the risk for migrant female farmworkers to develop health problems.

Objectives

The primary objective of this cross-sectional hypothesis-generating study is to investigate the reproductive health of an under-served population of minority, largely Hispanic women (aged 18-45) living in California farmworker communities. The specific aims of this study are:

1. To conduct a cross-sectional survey of women living in California farmworker communities, 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 and compare the prevalence of specific gynecologic and reproductive health problems in female farmworkers engaged in different specific farmwork activities.
4. To determine the prevalence of post-natal problems experienced by the study women and

their infants and any relationship to specific occupational farmwork activities.

5. To review and refine the study design, study instruments, and community approaches during the course of the different studies in different agricultural regions in California.

Methodology

The study will be implemented in several stages. A pilot study has been initially 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 us in developing the most accurate, acceptable and comprehensible bilingual, bicultural approach.

The basic study approach: After a farmworker community was chosen, the sampled area was divided into enumeration districts, including both urban and rural areas. After sampling several enumeration districts, these areas were exactly mapped out showing the precise locations of the dwellings in each parcel of land for later enumeration purposes. From each sampled and mapped block, dwellings were randomly chosen and their occupants enumerated for further interviewing purposes. Female occupants were randomly sampled after the enumeration and an extensive interview using a pretested questionnaire was administered by bi-cultural and bilingual interviewers. After the interviews were implemented and the questionnaires reviewed for completeness, the answers are being coded and put into a computerized data base. Furthermore limited physical examinations were conducted in the community clinic to determine weight, height, pulmonary function as well as limited medical tests to assess hematocrit and other hematologic values and urinalysis.

Statistical data analysis of the interview-based findings and the lab-based findings will follow data entry. The analysis will focus on the association of reproductive health outcomes with exposure to farming activities. Women not employed as farmworkers will serve as the comparison group in the study. Specific variables of interest are menstrual cycle irregularities, abortion, premature deliveries, pregnancy complications, and abnormal post-natal development of infants.

The final results of the pilot study will be used to plan and implement the full-scale study in several other agricultural regions of California which will begin at the end of 1993.

Significant Findings

From July to mid-September 1992, the pilot study was implemented in Parlier, a community in the Central Valley of California. Before the major and time-consuming step of coding and entering all the collected information into a database will take place, a initial review of the questionnaires lead to the extraction of some demographic information. The following results are available: The overall participation rate in the pilot study was about 75%. Of all the interviewed participants, 78 (52.3%) were females. The majority (70.5%, 17.4%) of participants considered themselves "Mexicano/a" or "Chicano/a" respectively. 66% of all participants had done farmwork in the last year. Most female respondents (81%) had at least one pregnancy.

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 (CS₂) 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 CS₂.

Methodology

The principle in developing biomarkers for exposure to *n*-hexane and CS₂ is based on the reactivity of the *n*-hexane metabolite, 2,5-hexanedione (2,5-HD), and CS₂ 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. CS₂ reacts with lysyl amino groups to yield dithiocarbamates. We have developed monoclonal and polyclonal antibodies to bovine serum albumin (BSA)-pyrrole derivative of 2,5-HD.

Studies on antibodies for BSA-bound CS₂ 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 CS₂. 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 CS₂ 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

CS₂. Since the neurotoxicity of both *n*-hexane and CS₂ 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.

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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 which is clinically significant and disproportionately greater than that which might result from either variable alone. Older, retired adults who were routinely exposed to solvents during their working years may therefore be at increased risk for significant neurologic problems attributable to their former work even though such problems may have been inapparent during the earlier periods of solvent exposure.

Objectives

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

Significant Findings

None to date.

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 from PCE source, (2) PCE air levels, (3) PCE breath levels. Full-shift continuous PCE peak sampling (Bruehl 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 (R_xT). 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

<u>Function</u>	<u>Mode</u>	<u>Test</u>	<u>Method</u>
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.

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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

None to date.

Organophosphate Neuropathy and Biomarkers of Exposure

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Funding Level: *\$53,987 (\$53,987 Cum)*

Importance to Occupational Safety and Health

Poisoning with methamidophos and certain other organophosphate insecticides 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. We propose to validate this assay among a population of poisoned workers. The assay is potentially of use for screening workers exposed to organophosphate neurotoxins, for predicting the clinical sequela among individuals poisoned with methamidophos 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 chronic subclinical peripheral neuropathy caused by methamidophos, and that this syndrome can be reliably detected by electrophysiologic assessment of sensory and motor function coupled with assessment of methamidophos 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.
2. Whether previous poisoning with methamidophos 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.
4. Whether there exist threshold levels of methamidophos exposure below which either sensory or motor neuropathy is no longer evident.

Methodology

The study population will consist of 50 previously poisoned agricultural workers identified at two teaching hospitals in Nicaragua plus two control groups: (1) community controls — many of whom apply pesticides, but have never been poisoned — and (2) unexposed cattle rancher controls. At the time of poisoning inhibition of neuropathy target esterase (NTE), the putative target enzyme for organophosphate neuropathy, will be measured in peripheral lymphocytes. Poisoning by methamidophos will be confirmed by measuring erythrocyte and plasma cholinesterase, and by

measuring methamidophos residues in dermal wipes. Severity of poisoning will also be evaluated clinically. One and one half years later these workers and their respective controls will be examined using a standardized, comprehensive neurologic examination. Cutaneous quantitative vibrotactile threshold (index fingers and great toes bilaterally) will be measured, as an index of large fibre dysfunction, using the Vibratron II instrument (Sensortek, Clifton, New Jersey). Thermal threshold will be determined using the NTE-2 (Sensortek, Clifton, New Jersey) as an index of damage to small, unmyelinated nerves. Upper extremity grip strength will be measured using a Pinch Gauge (B & L Engineering, Santa Fe Springs, California). Electrophysiologic studies of the ulnar, tibial, and sural nerves will be performed on the non-dominant limbs on all subjects. Sensory studies utilizing antidromic stimulation will be performed on the ulnar and sural nerves; motor studies will be performed on the ulnar and tibial nerves. Outcome measures of interest include distal motor latency, compound motor and sensory nerve amplitude, conduction velocity and late response F waves and H-reflexes for each nerve tested.

Significant Findings

None to date.

The Effects of Impulse Noise on the Auditory System

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 Start & End Dates: *07/01/80 - 03/31/96*
 Funding Level: *\$243,115 (\$1,606,354 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. Hearing is tested, the animal is exposed to impulse/impact noise, and its hearing is tested at regular intervals over the

following forty days. Routine data collection consists of measurements of hearing sensitivity, auditory discrimination, and cochlear histology. More detailed studies of certain experimental groups will include scanning 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) Recent work has shown that certain low level exposures may actually protect the subject from further exposure to dangerous noise. All of these results have direct implications for the management of workers in noisy environments.

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Functional Correlates of Cochlear Injury

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Start & End Dates: *06/01/90 - 05/31/93*
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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 will address the interaction between aging and noise-induced hearing loss.

Studies of complex signal processing (i.e., psychophysical tuning curves, differential thresholds for frequency and intensity) in young and old and normal and noise damaged chinchilla ears help determine the relation between cochlear damage and other more subtle measures of hearing which may not be as robust as the pure-tone threshold, and thus better predictors of cochlear damage.

Acoustic measures made from ear canals of unanesthetized chinchillas (otacoustic emissions and acoustic intermodulation distortion products) 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 11 computer system. Acoustic measures are made with small probe microphones and receivers positioned in the ear canal of the unanesthetized animal. Audiometric 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 long periods

do not suffer additional 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. Measures of intensity difference limens and acoustic intermodulation distortion products made few differences in young and old chinchillas: old animals detect intensity increments nearly as well as young animals, and have nearly as robust acoustic intermodulation distortion products.
8. Evaluation of portions of the ANSI-S12.13 database that are labeled as "low noise" has revealed that U.S. male workers exposed to noise below 85 dBA TWA in their most recent job have hearing levels considerably worse than the levels identified as representative of a nonoccupationally exposed control population in the ISO R 1999 standard (Annex B). However, some of the individuals may have had previous occupational noise exposure and may be misclassified as low noise exposed. Annex B was verified with data from original sources and, in the process, three transcription and calculation errors were corrected. Interestingly, hearing level differences between female workers and the control population were very small, suggesting that U.S. females have considerably less exposure to nonoccupational noise than males. Nevertheless, these findings indicate the need for more carefully controlled industrial surveys to determine the appropriate control population for U.S. workers because the ANSI-S12.13 database was not developed for the purpose of defining a control population.

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Hearing Hazard Associated with Industrial Noise Exposure

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Importance to Occupational Safety and Health

Many industrial noise environments are characterized by high levels of impact noise that are superimposed on a continuous background noise, thus producing a complex temporal signal. The limited demographic data and a large body of experimental data show that many of these "complex noise"

environments pose an unusually high risk of hearing loss to the repeatedly exposed individual. The need exists to develop metrics which can be extracted from such "complex noise" environments for use in objectively estimating the hazards that such environments pose to hearing. Our research efforts are directed toward such a goal. Our experimental approach will yield a generalized methodology that can be used to model and evaluate all forms of industrial noise environments and holds the promise for producing analytical procedures that can be incorporated into a new generation of measurement equipment for use in estimating the hazards posed by virtually any industrial noise environment.

Objectives

There are three goals to the current three-year research program: (1) to develop a model digital noise generation system which can be used to reproduce the essential characteristics of high level, non-Gaussian industrial noise environments. The system which has been built incorporates features such as multiple impact sources and room reflection characteristics to produce "complex" noises whose statistical properties can be controlled; (2) to explore the applicability of new approaches to signal analysis such as, adaptive noise cancellation, frequency domain kurtosis, and cepstral analysis to quantitatively evaluate non-Gaussian noise environments for the purpose of hearing conservation; (3) to expose experimental animals (chinchillas) to "complex noise" paradigms that are designed to explore which metrics of a "complex noise" environment are suitable predictors of the hazard to hearing following prolonged exposures. The noise exposures are being designed to test the hypothesis that non-Gaussian noise is more hazardous to hearing than is a Gaussian noise exposure of the same amplitude spectrum and total energy, and that this effect is frequency specific.

Methodology

An approach to digital noise generation has been developed which is capable of producing noise whose statistical properties and spectrum are under experimental control. The basic idea is that the desired noise is designed in the frequency domain by manipulations of the phase spectrum. In essence, once an amplitude spectrum is chosen, phase spectrum manipulations can produce peaks in a continuous noise which derive their energy from any selected portions of the amplitude spectrum. Results indicate that entire families of noises having the same spectrum but continually varying statistical properties can be created. Noise environments similar to bottling, stamping, punchpress operation, etc. can be

modeled. Software has been written to perform frequency domain kurtosis computations and cepstral analysis on non-Gaussian noise signals. These analytical measures are being explored because of their potential to provide a metric that can be used to assess the hazards to hearing from exposure to non-Gaussian industrial noise environments. Chinchilla are being exposed for five continuous days or on an interrupted daily schedule to various complex noises. Hearing thresholds are obtained prior to exposure and at regular intervals following exposure using brain stem (inferior colliculus) evoked potentials. Sensory cell populations are obtained from each animal using surface preparation histology or scanning electron microscopy, and relations among noise metrics, audiometry, and histology are derived.

Significant Findings

1. A digital noise generation system which relies upon manipulations of the phase spectrum can be successfully used to produce noise exposure stimuli of constant energy, fixed spectrum, and a variable kurtosis. The system which is designed to generate non-Gaussian signals in "real time" can effectively simulate a wide variety of complex industrial noise environments.
2. Experiments using the above system to generate relatively low levels (90 and 95 dB SPL RMS) of noise have shown that there are up to 20 dB statistically significant differences in permanent threshold shifts produced by Gaussian and non-Gaussian continuous noise exposures of the same total energy and spectrum. The non-Gaussian exposures produced the greater loss. While the audiometric profile of the animals exposed to the Gaussian noise was what would be anticipated on the basis of the spectrum of the noise, this was not the case for the animals exposed to the non-Gaussian noise. For these latter groups PTS at frequencies above 4 kHz were up to 20 dB greater than in the Gaussian exposures. This is surprising since the spectrum of the exposure contains very little energy above 4 kHz. This result parallels the findings from human temporal bone studies that show severe noise-induced degeneration of the Organ of Corti in the extreme base of the cochlea despite the probable lack of noise exposures at such high frequencies. At higher noise levels (up to 107 dB SPL) there are still differences between pure impact noise exposures and equivalent Gaussian noise exposures with the former producing more (up to 10 dB) PTS at most audiometric test frequencies but the high frequency effects discussed above were not seen.
3. It is clear that the long term average spectrum of a noise typically measured in industrial noise

surveys can in cases of non-Gaussian noise exposures provide a misleading analysis. Application of frequency domain kurtosis to such noises will provide an indication of which portions of the noise spectrum are undergoing the largest fluctuations as a result of the presence of intermittent impacts. The kurtosis spectrum is however very dependent on the temporal structure of the impacts and their temporal pattern. As a result, the kurtosis spectrum is not always easily interpreted.

4. When impact exposures are presented on an interrupted schedule of 6 hr/day for 20 days (i.e., total exposure energy is the same as that used in the 5-day exposures) daily post exposure thresholds improve by up to 40 dB over the first five days of the exposure protocol. The magnitude and time course of this effect is dependent on peak SPL of the impact, and on the prior history of noise exposures.

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Prediction of NIPTS, Hearing Impairment and Handicap

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Importance to Occupational Safety and Health

Knowledge of the valid relations between measures of exposure to industrial noise and permanent loss of hearing sensitivity, as measured by noise-induced permanent threshold shifts, NIPTS, is of importance to the setting of limits for exposure to noise and the specification of hearing conservation programs in industry. Quantified knowledge of the relations between hearing impairment, as assessed by NIPTS, and handicap for understanding speech under typical living and work conditions is of importance to the setting of criteria of acceptable degrees of hearing loss. Firm scientific understanding of, and agreement on, these matters are lacking.

Objectives

The project has two major objectives:

1. To establish as valid a base as possible for the writing of technical methods and standards for predicting the amount of hearing loss, NIPTS, to be expected in persons exposed to industrial, and other noise and sound; and
2. To provide quantitative information about the ability of persons with specified amounts of NIPTS to understand speech, as measured by sentence tests, and to hear and understand speech in everyday living conditions.

Methodology

Objective 1. A re-examination is being made of the basic data from the major research studies that were designed to show the amount of NIPTS to be expected from exposure to industrial noise of specified durations, intensities, and years of exposure. Included in this examination are the specifications, and their bases, provided in recently standardized methodologies, ISO Standard 1999, 1991, for making such predictions. Data from ISO 1999, and the hearing levels of noise exposed and, when provided, non-noise exposed "control", workers from ten major studies have been placed in computer files for statistical analysis. All the data have been adjusted to be relative to audiometric zero as given in ISO Standard 389, and for manual audiometry. Tables and graphs comparing the data of the different studies, and possible explanations for any major differences among the findings, will be prepared.

Objective 2. During the years of 1971-1975 the U.S. Public Health Service administered pure-tone hearing level and sentence intelligibility tests to a random sample of adults in the United States. In addition, the subjects were asked to rate their hearing in each ear, on a scale from "deaf" to "good", and whether they could usually understand what a person was saying across a room when speaking in a "whisper", a "normal voice", and a "shout". These, and related relevant data, have been placed in VAX main-frame computer data files. The speech intelligibility and self-ratings data have been coded to permit zero-order and multiple regression analyses with each other, and with the hearing level thresholds taken at separate frequencies and in various combinations.

Significant Findings

Objective 1. Reviews of research and re-analyses of data pertaining to the hearing levels of workers exposed to 8-hour workday steady noise,

and methods for predicting NIPTS from such noise, have been completed. Significant findings are:

1. The effects of two noise exposures, such as factory and gun, is a function of the sum of the sound energy in the two noises, and not the sum of the NIPTS to be expected from each noise separately. This factor, and the effects of nosocosis on hearing levels, have obfuscated true amounts of NIPTS found in some previous studies of workplace noise.
2. A quantity EEA (Effective Energy, A-weighted), based on 8 log years of noise exposure better predicts NIPTS than present standard 10 log exposures years formula.
3. Threshold, for unscreened S's median 0 dB NIPTS, 4 kHz, 8-hour day exposures to steady work noise, is about LAeq8h 90 after one year, and 76 after 50 years of exposure.
4. Threshold, for screened S's for median 0 dB NIPTS, 4 kHz, 8-hour day exposures to steady work noise, is about LAeq8h 80 after one year, and 66 after 50 years of exposure.
5. NIPTS values predicted by Robinson's EA formula for estimating NIPTS is believed to underestimate NIPTS because its data base involved a volunteer-subject selection process that may have excluded workers who had the higher amounts of hearing loss.
6. A synthesis curve was drawn, and a mathematical formula derived, that describes, as a function of EEA, NIPTS found for all studies of screened subjects, except in case of EA.
7. Compared to EEA, the recent (1990) ISO Standard 1999 underestimates by 1 to 16 dB, depending on test frequency, NIPTS to be expected from exposures to steady noise.
8. The data bases (EA and Passcheir-Vermeer models) of ISO 1999 are of questionable validity due to possible data bias in subject selection, and inadequate data processing.

Objective 2. The work done towards Objective 1 far exceeded the efforts as first estimated for the Grant. As a result, only regression coefficients among the variables in, and created from, the U.S. Public Health Survey have been completed. A Grant request to complete Objective 2 and analyze related nosocosis data has been submitted.

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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 is being 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 [³²P] 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 are being correlated to each other and 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 [³²P] 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 [³²P] postlabeling.

Significant Findings

Monoclonal antibodies have been developed against BP and its metabolites from the spleen cells of animals immunized with BP covalently coupled to carrier protein. These antibodies were characterized in terms of sensitivity and specificity by competitive ELISA. The ELISA has a 50% inhibition of antibody binding at 4 pmole of BP/well. There is 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.

An immunofluorescence method has been developed for the localization of adducts in skin biopsies. Staining with the PAH-DNA adduct specific antiserum followed by fluorescein labeled secondary antiserum indicated specific nuclear staining in biopsies of coal tar treated patients. Biopsies from untreated controls were negative. Adducts were also measured by [³²P] postlabeling of DNA isolated from the biopsies. Multiple hydrophobic adducts were seen in all biopsies of patients but not in controls. The immunohistochemical method should be applicable to the detection of adducts in biopsy material since small amounts of tissue are required.

All assays on DNA and protein adducts in blood and metabolites and mutagens in urine have been completed. Data is currently being analyzed for differences with exposure group as well as correlations between the different markers.

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Stress in One Occupational Group: Teachers

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Importance to Occupational Safety and Health

Van Wyck Brooks wrote that "Emerson advised his fellow-townsmen to manufacture schoolteachers and make them the best in the world." It would be difficult to think of another profession that is as important to producing tomorrow's physicians, scientists, and engineers. This longitudinal study, which was supported by NIOSH/CDC, assesses the effects adverse working conditions commonly encountered by newly appointed women teachers exert on their psychological health, health behaviors, and morale.

Objectives

1. To compare the mental health (e.g., depressive symptoms, self-esteem) 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., tranquilizer use), and morale (e.g., job satisfaction) of new 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 variety of social resource, namely, social support from colleagues.

Methodology

The project recruited subjects from two types of senior-year college classes: education classes that students typically take en route to teacher certification

and psychology classes that are largely taken by students with little intention to enter 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). With the Time 0 survey, the project collected critical preemployment data on the various outcome measures (e.g., depressive symptoms, motivation to be teacher) including expected job satisfaction. Outcome data and data on working conditions were collected during Time 1 and Time 2. Although data were collected for two additional years, I will not report on those data here because the project is still involved in data entry.

Significant Findings

The findings presented here include women teachers who met two criteria: they taught full-time in both the fall and the spring and did not change schools during that period. Women who taught part-time and women who changed from one school to another were excluded. The purpose of this exclusionary strategy was to examine women with the least ambiguous exposure histories.

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 symptoms levels.
3. Further analyses with statistical controls for preemployment factors, social demographic characteristics, and nonwork stressors indicated that adverse school conditions were related to

depressive symptoms, motivation to remain in teaching, job satisfaction, tranquilizer use, and self-esteem. The effect of working conditions on depressive symptoms was large enough to warrant public concern. These analyses tended to show that social support from nonwork sources was related to fewer problems; however, social support from work sources was not helpful in alleviating problems. The most important factor predicting the winning of social support from new colleagues was social support from outside sources. The personality factor locus of control was not related to the outcomes.

4. Individual coping behaviors were not related to reduced problems. The effects of coping behaviors were swamped by the quality of working conditions.

Conclusions. The factors that 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" and 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. It is important that we make every school safe and well run.

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A Laboratory Model of Sick Building Syndrome

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Importance to Occupational Safety and Health

Since the 1970's increasing numbers of buildings have been designed and constructed to conserve energy and reduce air conditioning and heating costs by minimizing air leakage through the building envelope. Concern has arisen that such construction practices may compromise indoor air quality and pose a threat to worker health. The term "sick building syndrome" (SBS) was coined to describe complaints that occur in these workplaces and lack a specific etiology, as in Legionnaires Disease or hypersensitivity pneumonitis. Among the agents thought to contribute to SBS are odorous volatile organic compounds (VOC).

Objectives

There have been relatively few attempts to study SBS under controlled laboratory conditions. The objectives of this pilot study were to test the feasibility of measuring changes in physiological, biochemical, cytological and neurobehavioral parameters that might underlie the symptoms of SBS during controlled exposure of volunteers to VOC.

Methodology

The project had two stages. During Stage 1, we assembled different components of the model step by step, as follows:

1. We measured the fractional retention of VOC by the respiratory system during brief periods of exposure, plus measurement of their excretion in expired air following two hours of continuous exposure. The measurement of fractional retention combined with the measurement of total ventilation, obtained by inductive

plethysmography, were used to calculate total retained dose. The latter together with the post-exposure measurements of respiratory excretion lay the groundwork for toxicokinetic analysis.

2. We developed preliminary data on possible relationships among the following: ambient concentration of two irritants (acrolein, mixed VOC), conjunctival symptoms, and changes in composition of tear fluid. Acrolein was administered by means of safety goggles modified for this purpose. The goggles were intended to limit the conjunctival response to a direct effect by eliminating the possibility of respiratory-initiated reflexes that affect tear fluid formation.
3. We explored the possible addition to the model of cognitive testing along with an assessment of glucose metabolism in selected brain regions (neocortex, basal ganglia, and cerebellum) using a radiotracer, ^{18}F -deoxy-glucose. The technique utilized a dual-probe positron detector that allowed a significantly lower dose of radioligand than is required by positron emission tomography (PET).

In Stage 2, preliminary results were obtained on each model component on from 1 to 8 subjects. The subjects were either healthy non-smokers with no history of SBS, or subjects with a history of SBS, a diagnosis of multiple chemical sensitivities (MCS) and symptoms germane to the assay being tested. Six subjects visited the laboratory on three separate days. Day 1 was devoted to (1) orientation/preparation, (2) practice of neurobehavioral tasks, and (3) questionnaire completion. On Days 2 and 3, measurements on tear fluid, neurobehavioral tasks and symptoms were made before, during, and following exposure to clean filtered air or mixed VOC. Exposures were conducted in a whole body chamber.

Significant Findings

1. We found that excretion after exposure to two VOC, toluene and n-hexane, was rapid. In the case of toluene, excretion appeared to be biphasic in character; an initial brief phase of rapidly declining excretion lasting minutes, followed by a more prolonged phase of excretion at a low rate. A rapid short-lived excretory phase from the respiratory system was also observed for n-hexane, but not a slow phase, reflecting perhaps the limited sensitivity of our analytic technique. These findings suggest that expired gas samples may not provide reliable quantitative information on the level of exposure to these particular VOC, even in the event of recent

intense dosing. Markers of metabolic transformation, such as might be present in urine or blood, might prove more revealing.

2. We developed a simple, relatively noninvasive procedure for collecting tear fluid to assess possible changes in fluid composition following exposure to irritants. We found a suggestive increase in total protein and LDH relative to baseline in the tear fluid of subjects exposed to acrolein and VOC who reported eye irritation during exposure. The use of goggles to administer the pollutant permits assessment of direct conjunctival effects as well as the study of agents that may be too hazardous to be inhaled.
3. We tested an environmental chamber analogue of Sick Building Syndrome based on a mixture of 3 VOC often present in the air of new or remodeled buildings, at a realistic concentration ($<20\text{mg/m}^3$); we confirmed the validity of this analogue by determining that subjects without a history of building-related illness reported relatively few symptoms whereas subjects with a history of building-related illnesses reported a relatively large number of symptoms post-exposure. Moreover, we observed a progressive increase in symptoms during a 2 hr exposure to the mixed VOC in both historically sensitive and control subjects, whereas symptoms in both groups either were unchanged or decreased during a 2 hr exposure to clean filtered air.
4. We found that exposure to mixed VOC, but not to filtered air, produced a disproportionately large incidence of symptoms referable to the CNS and increased errors on two cognitive tasks in historically sensitive subjects, but not in control subjects.
5. We found that dual probe analysis, an experimental procedure for measuring glucose metabolism over time in different regions of the CNS, as currently performed, is not consistently reproducible and is excessively confining and uncomfortable. Current work combining bolus injection with continuous infusion of the radiotracer is under way to reduce the time required to obtain data and to improve reproducibility of the measurement.

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 devices on the underground mine environment.

Objectives

The overall objectives of this project are: (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 $\leq 1 \mu\text{m}$ in size were considered to be primarily of diesel origin. A sampler was located at the section intake and operated up to six hours/sample. Another Hi-volume sampler was placed in the haulageway near where diesel shuttle cars turned around to dump their loads. The sampling times varied between 8–30 minutes and were only collected during periods of diesel activity. 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.

During the last year of this project, samples have also been collected and analyzed using similar techniques from a metal mine when diesel vehicles were operating with and without a combined DPM control device, i.e., a catalyzed diesel particle filter (CDPF) and an oxidation catalytic converter (OCC). These devices were used in combination in an attempt to lower DPM levels by reducing both the solid component and the associated organics.

Laboratory samples for DPM and semi-volatile organics were collected at the BOM in two separate studies: (1) with and without a CDPF; and (2) with and without an OCC. Both 508 x 508-mm filter (DPM) and XAD-2 resin (XAD-2 resin organic component or XOC) samples were collected. The organic material associated with both types of media was removed by Soxhlet extraction with dichloromethane. The CDPF studies were conducted using a low sulfur (0.039 wt.%) 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 represent potential highest in-mine values that would occur when diesel

equipment is operating in a given area. The DPM values (mean/mine range of 0.9 – 1.9 mg/m³) are 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 are 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. These values will be compared to those obtained from a coal mine where a DPM emission control device is in use (samples to be collected in December, 1992).

The differences in levels between the mines are likely related to differences in parameters such as vehicle type, mine ventilation efficiencies, fuel composition, and engine design, operation, and maintenance. Our general observation is that engine operation and maintenance is probably 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 can be used to estimate in-mine levels in dieselized underground mines, based on the statistical comparisons between diluted (100:1) laboratory data and underground coal mine ambient pollutant data. 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. We found that the laboratory data obtained from a transient cycle designed to simulate haulage vehicle operation closely resembled the coal mine data where such haulage vehicles operate. The laboratory 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, use of this 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 is slightly less effective in reducing vapor phase organics compared to SOF (99 percent versus 89 percent, respectively). However, both reductions are significant. The CDPF removal efficiency for DPM-associated PAH is ≥ 98 percent for both transient and steady-state operation. Only two (fluoranthene and pyrene) of the seven PAH were found with the vapor phase organics with or without the CDPF. Slightly lower reductions of these PAH with the CDPF were also found compared to the

PAH reductions found with the SOF. Over the transient cycle, the CDPF reduces the DPM-associated mutagenicity levels by 75 percent and the vapor phase organics-associated levels by 80 percent. The steady-state weighted cycle produces 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) may be related to presence of other active compounds such as nitro-PAH.

When used in conjunction with a low sulfur fuel, use of this OCC in underground mines could also have a significant impact on reducing DPM levels as well as other emission components. For this study, a transient test cycle was selected to simulate potentially worst case operation of the OCC. From 30 to 60 percent reductions were found in DPM, SOF, vapor phase organics, and mutagenicity and PAH associated with the SOF and vapor phase organics. Typically, engines in underground mines would be operated at higher loads and greater reductions in DPM and many other emission parameters would be expected. Some differences in emissions due to fuel composition were also noted.

Effects of DPM Emission Control Devices as Measured in Underground Mines – Use of a combined CDPF/OCC in an underground metal mine resulted approximately 50% reductions in DPM and SOF concentrations. This is based on samples collected only when the diesel front-end loader vehicles were operating; however, a similar reduction in DPM levels was found by BOM personnel using personal-type samplers. The less than expected DPM reductions (based on data from the laboratory studies) may be due in large part to the nature of the actual mining operations. The area where the diesel with the control device was operating was heavily impacted by air from other areas in the mine where dieselized vehicles without emissions control devices were in use. In the same study, mutagenic activity concentrations (revertants/m³) increased by about 250% with CDPF/OCC use, reflecting over 500% increases in activity on a mass basis (revertants/ug SOF). This increase is possibly due to increases in nitro-PAH with use of the CDPF component of the control device.

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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

Galerkin and/or Petrov-Galerkin finite element techniques will be used initially to approximate the three-dimensional velocity and concentration fields. Validations will include hot-film anemometry, flow visualization, and concentration measurements using sulfur hexafluoride as a tracer. Infrared spectrophotometry will be the detection method.

Significant Findings

A finite element code has been developed for the prediction of the three-dimensional velocity and turbulence kinetic energy fields generated by a coaxial turbulent square jet and square hood in the presence of a cross draft perpendicular to the common centerline. The code relies on reduced quadrature to upwind the convective term and a penalty formulation to eliminate pressure. 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 good agreement with computer simulations.

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 catastrophes 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 3000 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

We have demonstrated that in most fault diagnosis problems, the fault classes form tightly bounded regions in the space of input units. Hence, one requires neural net classifiers that can represent bounded fault classes. It turns out that linear activation function based neural nets are not suitable as they cause non-robust classification. These nets use hyper-planes in the input units space to carve up the space into various regions and make them correspond to the different fault classes. Since the hyper-planes are open ended, they lead to regions that are not well-bounded and this leads to generalization problems. We have also shown that these problems can be circumvented by using an ellipsoidal activation function for the hidden nodes, as they generate bounded fault classes.

On the problem of extracting key qualitative features from noisy data, we have developed a hierarchical representation that can model process trends at different levels of detail. A neural network technique for identifying the various classes of trends from noisy time series has also been achieved.

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 (chrome 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 are being carried out consisting of 12 1-hour sampling periods which will also include measurements of general and local exhaust ventilation.

Methodology

In the first two years of the study we have carried out field tests under production conditions 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

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.

Computational Methods in Industrial Ventilation

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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 the existing algorithm to improve speed and flexibility. Sulfur hexafluoride tracer gas studies will be conducted using infrared spectrophotometry to validate exposure estimates. Smoke wire techniques and helium filled bubbles will be used to explore flow patterns 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 is underway to select optimal parameters and evaluate the stability and convergence of the algorithm. Wind tunnel studies to collect data for model validation are also beginning. A Lagrangian particle tracking algorithm for estimating tracer gas concentration fields has been incorporated with the DVM code. Predictions of concentration are in reasonable agreement with measured values, but work is needed to specify small-scale turbulent time and length scales.

Field Study of Local Exhaust Ventilation Performance

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Importance to Occupational Safety and Health

A model which can be used to predict capture efficiency for flanged slot hoods exhausting area sources in the presence of a uniform crossdraft has been developed and validated under controlled laboratory conditions. This project will field validate the capture efficiency model for vapor degreasers exhausted with exterior type hoods, quantify industrial crossdrafts, and correlate process and worker activities with capture efficiency and crossdraft measurements.

The research will lead to (1) an improved method for predicting hood capture efficiency and improved hood design methods; and (2) a better and more systematic evaluation of industrial crossdrafts, including the turbulence characteristics of these crossdrafts. Improved hood design methods, combined with a better understanding of the characteristics of industrial crossdrafts, will result in improved air quality in plants using vapor degreasers, lower probability of health hazards and safety hazards

associated with air concentrations of halogenated solvents, and possibly lower operating costs if the solvent is recovered from the local exhaust system.

Objectives

The broad long-term objective of this research is to answer the question: Can exterior hood design be improved to adequately control emissions from open surface tanks? The specific aims of the research are to answer the following questions: (1) Can laboratory validated capture efficiency models be used to predict capture efficiency of local exhaust hoods in industrial settings? (2) Can industrial crossdrafts be quantified and characterized? (3) Can activity parameters be correlated with measured crossdrafts and capture efficiencies?

Methodology

The project involved conducting seventeen field studies. Three sets of measurements were done during each study to answer the questions asked in the specific aims.

Solvent concentration was measured in the duct and at several distances from the degreaser. This allowed for calculation of solvent emission rates from Fick's Law and the concentration gradient or other appropriate mass balance models including the completely mixed space model. The duct concentration and the emission rate allows for calculation of capture efficiency. During idling conditions, tracer gas was released through a diffuser sized to fit into the degreaser. Sulfur hexafluoride (SF_6) was released at a measured rate and the concentration of SF_6 was measured in the duct downstream of the hood. The duct air flow was measured, along with the hood and tank dimensions. These measurements allowed for the calculation of capture efficiency. The SF_6 measurements were limited to idling conditions because the SF_6 release apparatus would interfere with operation of the degreaser. The emission rate approach was used to measure hood capture efficiency during production times.

Crossdraft velocity (magnitude, direction, and turbulence parameters) was measured simultaneously with measurement of capture efficiency using a TSI, Inc. two-dimensional hot-wire anemometer with high frequency response suitable for turbulence measurements. The anemometer signal was recorded through an analog-to-digital converter by a Toshiba T5200 personal computer.

Capture efficiencies measured each hour will be compared with model predictions. The magnitude of the crossdrafts will be tabulated for use in the design and operation of local exhaust systems as well as design of future experimental work. The turbulence

characteristics of the crossdrafts will be analyzed to determine how close (or different) they are from those used in the laboratory development of the capture efficiency model. The model may need to be adjusted for any significant differences.

Activities involving the degreaser (loading, unloading of parts; opening, closing of cover; size, shape of parts; etc.) and activities in the vicinity of the degreaser (workers walking, standing, sitting near the degreaser; use and location of cooling fans; location of general ventilation supply and exhaust openings; etc.) were recorded during each hour that sampling was conducted. Recorded activities will be correlated with recorded crossdrafts to determine how specific activities are related to measured crossdraft characteristics.

Significant Findings

The completely mixed space and the Fick's Law diffusion models can be used to estimate emission rates from vapor degreasers. Measured emission rates ranged from 0.24 to 14.1 g/min and measured capture efficiencies ranged from 67 to 100%.

Crossdrafts near local exhaust hoods can be quantified in the field. Measured crossdrafts ranged from 0.4 to 1.9 fps.

Measured crossdrafts can be added to existing flow field models and used to predict capture efficiency of local exhaust hoods. The measured crossdrafts resulted in predicted capture efficiencies ranging from 57 to 90%.

The predictive model for capture efficiency underestimates the measured values, indicating other factors, in addition to crossdrafts, need to be included in the model.

Full Circle Ergonomic Auxilliary Tool Handle

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Importance to Occupational Safety and Health

Full Circle Systems has developed a new design for tool handles. The new design allows the user to hold the hands perpendicular to the direction of the pull, with the point of contact being spread over a large area of the palm. The wrists are straight; both arms can be held low; and the back remains straight.

Use of this handle will reduce the occurrence of blisters, callouses, cramped muscles, sore backs, and cumulative trauma disorders. It may prevent disorders such as carpal tunnel syndrome, and it may allow patients with disorders, such as arthritis or diminished grip, to use tools more comfortably.

Objectives

The objective of the proposed research was to measure the effectiveness of the new handle as well as to answer specific questions concerning the detail of the handle design. This research helped insure that the new tool handle maximizes its benefit to a variety of users.

Methodology

The research entailed two types of tests. In laboratory tests, measurements of IEMG and force data were taken while subjects used test and control handles in simulated work environments. In a second set of tests, subjects used test and control handles in their real work environments. In both sets of tests, one-half of the subjects used the test handle first and half of the subjects used the control handles first. In both sets of tests, video recordings were made in order to measure the position of hands, wrists, arms, and back.

Significant Findings

The IEMG and force data collected confirmed two hypotheses:

1. When using the test handles, subjects can deliver more force while producing smaller EMG values, as compared with control handles.
2. When using the test handles, subjects can deliver more force and maintain the force longer before fatigue sets in, as compared with control handles.

The IEMG and force data collected also produced two findings that we had not anticipated:

1. Pushes and pulls are very different for both test and control handles. In general subjects tended to produce more force when pulling than when pushing on the Kin-Com machine. Many subjects showed a greater reduction in EMG when

pushing with the test handles and a greater increase of force when pulling with the test handles as compared with the control handles.

2. When using the test handles, subjects tend to use the muscles in both hands more evenly, as compared to the control handles; that is, when using the control handles the subjects tended to use their dominant hand (right side for right handed subjects) almost exclusively, but when using the test handles, these subjects tended to use both hands to push and pull.

The data collected at the work site confirmed two hypotheses:

1. Subjects tend to keep their wrists, arms, and back in anatomically more neutral positions when using the test handles as compared to using the control handles.
2. Subjects can more easily shift their body positions, including switching left and right hands, when using the test handles.

The data collected at the work site also produced two findings that we had not anticipated:

1. The test handles increase the subjects ability to twist the handles (i.e., apply torque). This is particularly helpful when using a dust mop because subjects had to twist the mop's pole in order to rotate the mop's head when getting around or under obstacles. This ability to apply torque more easily reduced fatigue for all subjects who used the test handle on dust mops and for some subjects who used the test handles on other tools. This ability to apply torque also meant that the handle must be secured very tightly.
2. We had expected the subjects would want to adjust the distance between the front and rear handles, but we were surprised to find out that subjects also wanted to adjust the angles of the front handle, and that this adjustment is very helpful for making the tool more comfortable and safer. We had planned to produce a non-adjustable version first and then come out with an adjustable version later. We determined that it will be best to come out with the adjustable version from the start even though it may be more expensive and complicated to manufacture.

These findings indicate that the test handle will be helpful to workers doing the same activity for long periods of time, especially if they can not take periodic breaks (e.g., farmers or migrant workers hoeing a field from sun up to sun down).

These findings also indicate that the test handle will be helpful to workers who are asked to shift

from their regular activity to a new activity for which their muscles may not be fully conditioned (e.g., when a maintenance worker who usually mops a floor is asked to shovel heavy wet snow).

Smart, Safe Scaffolding

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Funding Level: *\$49,650 (\$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 will 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 in the development of sensing systems and techniques applicable to the monitoring of construction site shoring and scaffolding. This work will be demonstrated at our in-house laboratory facilities as well as at a "real-world" major construction site. The resultant sensor system 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, the initial field tests will begin. The first telemetry unit will be designed, in which the sensor data will be sent via a twin wire transmission line. Once the alarm software has been developed, load cells will be obtained and the sensor system will be tested at an actual construction site. Simultaneously, we will begin developing our own load cells.

In the project's second phase, the data from our field test will be analyzed. We will then develop the software necessary to present the information to the site engineers in a clear and concise fashion. A second telemetry unit will be designed, which will transmit the sensor data via radio frequency waves (RF). We will then incorporate our own load cells with the telemetry unit, and begin laboratory testing.

Upon completion of our laboratory tests, we will begin our final field tests. During the final phase of this project, the integrated sensor system will be taken to an actual construction site. The parameters of the telemetry unit, such as the range and accuracy of the received data, will be determined. Our load cells will be evaluated for their ease in installation and removal, and for their reliability in a construction environment. The load cell data will be present to the site engineers for their evaluation. In particular we will be soliciting their opinions on the signal conditioning software, its ease of use, and the best presentation for the information they find most pertinent.

Significant Findings

None to date.

Active Seat Suspension to Control Low Back Injuries

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Program Area: *Control Techniques*
Grant Number: *1 R43 OH03018-01*
Start & End Dates: *09/30/92 - 03/29/93*
Funding Level: *\$32,613 (\$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 recurrence of vibration-induced fatigue and lower back injuries and disabilities. This seat must be relatively inexpensive and be capable of new or retrofit installation.

Methodology

This study will involve three major phases. These are:

1. Computer simulations will be used to test various control algorithms until an optimal method is determined. Realistic design component limitations will be carefully considered. Power

Spectral Density Analysis will be the primary outcome measure used for comparison between methods.

2. A prototype will be built based on the optimum design found in phase 1. This will involve modifying a commercially available seat with new components that can be actively controlled by computer. The sensors needed to provide feedback information (e.g. accelerometers) will be determined by the control algorithm selected.
3. Testing of this seat will include designing a pseudo-human (spring-mass-dashpot system) with similar primary dynamic properties. This will allow for objective comparisons between this new actively controlled seat and existing passive seat suspension systems.

Significant Findings

None to date.

New Methods for Quantitative Respirator Fit Testing

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Program Area: *Respirator Research*
Grant Number: *5 R01 OH01301-08*
Start & End Dates: *09/29/82 - 08/31/92*
Funding Level: *\$141,066 (\$981,435 Cum)*

Importance to Occupational Safety and Health

Several million air purifying respirators are in use in the U.S. A significant percentage of the American workforce is, therefore, relying on respirators to reduce the risk of inhaling hazardous industrial aerosols. OSHA guidelines specify respirator fit testing to ensure the workers' safety. Field studies have shown that the laboratory-measured quantitative fit factors relate poorly or not at all to the workplace protection measured during work performance. Fast, reliable, and low-cost fit testing techniques are needed to ensure that the chosen respirator provides adequate protection. Data are needed on the performance of respirators as a basis for new standard setting. In the health care industry, surgical masks have historically been used only as barriers to prevent exhaled particles from infecting a patient in surgery, but are increasingly being used today to protect the health care worker from airborne submicrometersized pathogens against which presently available masks are ineffective.

Objectives

The overall aim of this research is to study the basic mechanisms of air and aerosol penetration through face seal leaks and the filtering material, and to develop from this knowledge quantitative fit tests that are easy and inexpensive to perform. Two types of respirators in common use are studied: (1) disposable respirators which consist mostly or entirely of contoured filtering material and (2) half-mask respirators which have air purifying cartridges attached to an impermeable body of rubber or silicone. The study has been extended to research on masks used in the health care industry where the aerosol is more complex due to the shape of the

pathogens. Also, and even more importantly, the collected pathogens may grow and be reentrained which will be analyzed by use of new bioaerosol measuring techniques.

Methodology

For the disposable respirator research, a size-fractionating aerosol generator has been developed which can deliver a high fraction of large particles and a low fraction of small particles so that a statistically significant number of particles is sampled from inside the respirator cavity over a wide range of particle sizes. The particle size distributions are measured by a computer-based aerosol size spectrometer. For the half-mask respirators, pressure sensing attachments have been developed through which the face seal leak flow rate is determined. A field computer determines the fit factor. The new method is tested on respirators in actual use and is compared with available methods used on surrogate respirators. For the surgical mask research, the viable test pathogens that have deposited on the mask or penetrated through the mask will be measured by physical and biological means.

Significant Findings

Through use of a condensation nuclei counting technique for fit testing respirators, the traditional aerosol generator and exposure tent or booth are no longer needed. This simplification and cost reduction has increased the use of quantitative fit testing.

A commercial development (PortaCount, by TSI Inc.), based on this technique, is now in prominent use in the U.S. In order to further reduce cost and make fit testing widely available, techniques were developed that do not involve aerosols but measure the face seal leak flow as a measure of respirator fit. In the first development, the wearer removes his or her cartridges, and replaces them with a pressure sensor attachment. While holding his or her breath for a few seconds, the pressure inside the respirator changes as a function of leak size. This pressure change is, thus, a measure of face seal leakage. It was found, however, to depend somewhat on the pliability of the respirator body.

Another technique was subsequently developed, whereby the face seal leak flow is measured in another way: The cartridges are again removed, but a small pump is connected to the respirator cavity. A bypass valve, connected through a small flow resistance to the atmosphere, ensures that the maximum pressure inside the respirator is similar to the pressure encountered during normal respirator wear. If a leak exists, the pressure inside the respirator, which is monitored by a sensor, is less than this maximum pressure. The measured pressure

is, thus, a unique function of the face seal leakage and, therefore, a measure of fit. Through further research a dichotomous-flow fit-testing system has been developed that simultaneously measures the flow through the leak(s) and the respirator cartridge(s). This system is compatible for field use. By use of this system on humans it was found that the variability that is normally encountered in fit testing is largely due to changes in the leak size while fit testing. Thus, it is not possible to measure highly repeatable numbers during fit testing. As leakage may also occur through faulty exhalation valves, a valve testing technique was developed as well. Field tests revealed that such valves tend to leak in dusty environments which suggest that field testing of the respirator in use is more desirable than the basic fit testing now in use.

In order to develop a fit testing technique for disposable respirators (filtering facepieces), fundamental studies have been performed on the performance of these respirators. The experimental data have been modeled through use of equations reflecting the many removal mechanisms that occur in a respirator. The fundamental problem with filtering facepieces is the difficulty in distinguishing face seal leakage from filter penetration, since the two flows cannot be separated as one does with elastomeric respirators by using high efficiency particulate air filters in the cartridges (which changes the pressure inside the respirator and may, therefore, affect the face seal leak).

In order to be able to study the performance of filtering facepieces, a size-fractionating aerosol generator has been developed and used successfully. In order to sample the aerosol inside the facepiece without biases due to leak and probe locations, a high flow rate probe has been developed. With these technical innovations, the performance of different kinds of facepieces has been studied over a wide range of particle sizes, loading conditions, and differences in manufacture. It was found that the performance in the submicrometer-size range is highly dependent on the degree of electrical charging achieved during manufacture, and that the performance in the submicrometer range cannot be predicted by the performance in the larger size range, and vice versa.

Based on these findings, a fit testing technique has also been developed for disposable respirators. It makes use of the unique difference that has been found between the combined aerosol penetration through the filter medium and the leak site at low versus high flow rates. Much of the experience gained through research on industrial respirators has now been applied to research on masks used in the health care industry. New aspects of this work are the use and analysis of bacteria collected on the filter medium.

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Respirator Performance Model for Particulates

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Program Area: *Respirator Research*
Grant Number: *5 R01 OH01595-06*
Start & End Dates: *09/23/83 - 08/31/92*
Funding Level: *\$94,391 (\$430,985 Cum)*

Importance to Occupational Safety and Health

The ability of airborne particles to penetrate the filters, exhalation valves, and facial seal leaks of air-purifying respirators depends strongly on particle size as does the respiratory hazard associated with these particles. Thus, the actual protection obtained for airborne particles will depend on the particle sizes present in the work place environment. This study characterizes the affect of particle size distribution on the performance of representative single-use, half-mask, and full-face mask respirators. No general data exist to describe the performance of respirators as a function of particle size distribution. These projects will improve, extend, and validate the use of the computer model for characterizing and predicting respirator wearer's exposure. It is anticipated that when the model is fully developed it will be a useful tool for respirator research and a useful screening tool for respiratory protection programs.

Objectives

The overall objective of this grant is to extend our understanding of the affect of particle size on the performance of air-purifying respirators for protection against particulate exposures. This is accomplished through experimental measurement of filter, exhalation valve, and facial seal leak performance as a function of particle size and flow rate and the use of these data in a computer model to predict overall performance for a respirator based on QNFT measured leakage, airborne particle size distribution, and the work rate of the wearer.

The specific projects are: (1) To evaluate leakage of normal and impaired exhalation valves during inhalation. (2) To perform model validation measurements with human subjects wearing respirators. (3) To evaluate the performance of respirator filters as they become loaded with dust.

(4) To evaluate the penetration characteristics of facial seal leaks for full-face masks.

Methodology

Projects 1, 3, and 4 are performed using the laboratory test apparatus described in *AIHAJ*, 48, 836 (1987). Masks are mounted on a manikin and penetration or leakage is evaluated with an oleic acid test aerosol over the particle size range of 0.1 to 11 μm . In Project 1, monodisperse aerosols containing a fluorescent dye are used and flow is established with a breathing machine. Projects 3 and 4 use polydisperse aerosols under steady flow conditions. Penetration is measured with an optical particle counter or aerodynamic particle sizer. Project 2 uses human subjects. Facial seal leakage is measured with a quantitative fit testing apparatus. A polydisperse oleic acid test aerosol with a fluorescent tag is used. Concentration is measured inside and outside the mask and compared to that predicted by the model.

Significant Findings

The initial phase of this study included detail laboratory evaluations of respirator filter performance as a function of particle size and flow rate, and penetration of particles through facial seal leaks as function of particle size and pressure drop.

The evaluation of exhalation valves is complete. Leakage for clean valves ranges from less than 0.001 to .05%, increasing with work rate. A 0.1 mm foreign object on the valve seat can increase valve leakage by 2 to 3 orders of magnitude to about 1%.

An analysis of the effect of respirator dead space on averaged inhaled concentration concluded that the use of peak inhalation concentration in QNFT may overestimate average inhaled concentration by up to 45%, although this error would not exceed 15% for typical QNFT conditions. Use of full-cycle average measurements in WPF studies may underestimate average inhaled concentration by as much as 50%. Protection factors calculated by the computer model may overestimate by up to 45% inhaled dose for half masks and by up to 90% for full-face masks.

The experimental part of the model validation project is complete. Detailed respirator performance measurements were made for sixteen subjects at two work rates, two fit conditions, and two particle size distributions. Results show a correlation coefficient of 0.7 between measured total penetration and model predicted total penetration.

Tests of the effect of dust loading on filter performance have been completed. Three series of experiments, each using a dust with a different particle size distribution, evaluated the effect of dust loading on filter performance. Loading increases filter resistance, which increases facial seal leakage,

and also increases filter efficiency, which reduces penetration through the filter. The overall effect of loading on respirator performance depends on the extent of facial seal leakage and the exposure size distribution. In most cases there is an initial increase in protection followed by a gradual decrease. Protection factors can change by a factor of five or more as a result of loading. The increase in filter resistance and the decrease in filter penetration with dust loading is greater for unit loading of smaller size distribution dusts.

The experimental measurement of facial seal leaks in full-face masks is complete. Leaks were created by inserting 0.9 mm wires in the facial seal. Leakage as a function of pressure drop across the mask and particle size for full-face masks was approximately the same as for half masks.

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Respiratory and Thermal Physiology of Face Masks

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Program Area: *Respirator Research*
Grant Number: 5 R01 OH02564-03
Start & End Dates: 05/01/88 – 04/30/92
Funding Level: \$141,912 (\$396,175 Cum)

Importance to Occupational Safety and Health

Heat stress is a potential risk factor for workers wearing respiratory protective devices and impermeable protective clothing in hazardous environments. Such protective equipment impairs evaporative heat loss, feels hot, places a burden on the circulatory system, and can be worn for only a limited time. Devices to carry away body heat restrict mobility of the worker and add to the weight and expense of the equipment. Yet although currently available facepieces are hot and uncomfortable (Nielsen, et al., 1987; Gwosdow, et al., 1989), evaporative cooling of the outer surface has been found to reduce the skin temperature of the face and to improve the comfort of the wearer (DuBois, et al., 1990). Similarly, early attempts at cooling suits by evaporation of water from wet cloths placed on the outer surface have seemed promising, and therefore we decided to try evaporative cooling of impermeable protective garments to improve the comfort of the wearer and to extend the time before the wearer becomes too hot to continue work.

Objectives

The overall objective of this study has been to find out the factors that cause discomfort of respiratory protective devices, and to remove the source of this discomfort. Studies supported by this grant have shown that the air in face masks is hot and humid, that the skin temperature of the wearer's face increases, and that the unaccustomed warmth of the face is accompanied by discomfort which is reduced when the air around the face is cool and dry. When a cooler mask was constructed and older masks were modified to make them cooler, the discomfort disappeared.

Recent objectives have included extension of the concept of evaporative cooling of face masks to include evaporative cooling of impermeable suits, to

ascertain the effect on skin temperature and comfort during moderate exercise, with the objective of extending the period of time chemically protective garments can be worn before the wearer becomes too hot.

Methodology

Five physically fit subjects took part in this study. They wore cotton shorts, work trousers, a long-sleeved cotton shirt, shoes, and socks. The impermeable suit worn over these clothes was a medium-size yellow slicker with a hood. Three different types of wet cloth were used to cool the outer surfaces of the suit. The outer covers initially were either made of 1/8 inch thick felt cut and sewn as a hood and jacket, or else Handi-Wipe cloth (a thin, woven fibre, porous, wettable material) draped over the front, back, and hood of the impermeable jacket. Later, to cool a larger fraction of the body surface area, one subject whose body surface area was 2.13 sq.m exercised 5 times at 60 watts of mechanical work while wearing a wet hood, wet pajama top, and wet pajama trousers to cover the outer surface of the impermeable suit. Air velocity was set at 1 mph and later 4 mph. These garments were weighed before and after exercise. The rate of heat loss was calculated from the rate of evaporation.

An aluminum half-facepiece respirator fabricated with inspiratory and expiratory valves and covered with thin felt attached to its outer surface using 3-M adhesive was worn with the felt or Handi-Wipe covers. Thermocouples were taped to the skin inside the mask and suit. Skin temperatures and comfort votes were noted every 5 minutes.

Subjects exercised for 30 min on a Monark bicycle ergometer set at 60 watts in a temperature controlled room at 25.7°C and a dew point of 13°C (50% RH).

Significant Findings

Throughout the exercise period, the skin of the front and back of the chest was 2°C cooler when the outer covers were wet than when they were dry. The subjects also indicated they were cooler and more comfortable when wet rather than dry. Thermocouples attached elsewhere on the body (not under the parts of the suit cooled by evaporation) did not show this cooling effect. During exercise, pulse rate increased equally whether the cloths were wet or dry. Esophageal temperature also increased equally.

The face felt slightly cooler when the felt on the outer surface of the half-facepiece was wet than when it was dry. However, the face was not too hot or uncomfortable during exercise even when the felt on the mask was dry, because sweat on the face and condensation on the inner surface of the mask were

evaporated by the large minute volume of ventilation during exercise, carrying heat away from the face by evaporation from the skin and inner mask surface.

Total rate of heat loss from the yellow slicker covered by the wet pajama ensemble and hood at an air speed of 1 mph was 283 Cal per hr, SD 13, of which 24 Cal per hr was from the hood, 111 from the shirt, and 148 from the trousers. Psychophysical scaling factors for the body at the end of 30 min exercise when the suit was dry were "warm, uncomfortable, with moderate to heavy sweating", whereas when the suit was cooled with wet pajamas the body felt "comfortable, cool, and slightly sweaty". The pulse rate was 90 per min. Skin temperature of the chest rose to 36.2 with the pajamas dry, but only 34.6 wet; temperature of the thigh was 34.8 dry, but 32.6 wet. All these factors improved still further when the wind speed was increased to 4 mph.

The conclusion from these experiments was that it is possible to cool the body into the thermal comfort zone despite retention of sweat inside the suit during exercise. These observations need to be extended to hotter and more humid climatic conditions before it is known whether they pertain to workers under occupational conditions.

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Evaluation of Respirators for Asbestos Fibers

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Grant Number: *1 R01 OH02922-01A1*

Start & End Dates: *09/30/92 - 09/29/94*

Funding Level: *\$177,312 (\$177,312 Cum)*

Importance to Occupational Safety and Health

Results from this research should 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 respiratory protection of workers exposed to fibers. Improved designs of the respirators and test procedures for NIOSH certification will likely to help to reduce occupational exposures to manmade and asbestos 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, it is very important to know the efficiency of the respirator filters in relation to fiber dimension. 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 are most likely to 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. Comparison of filter penetration efficiencies for spherical particles and fibers under these conditions will 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

None to date.

Performance of Surgical Masks

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Program Area: *Respirator Research*
Grant Number: *1 R01 OH02948-01*
Start & End Dates: *09/01/92 - 08/31/94*
Funding Level: *\$139,897 (\$139,897 Cum)*

Importance to Occupational Safety and Health

Respiratory protection has become desirable or necessary to protect both patients and operating teams from airborne and dispersed bloodborne pathogens. This concern is forcing a reconsideration of the design of current protective devices. 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 surgical masks which have historically been used only as barriers to prevent exhaled particles from infecting a patient in surgery, but are increasingly used today in medical and dental care environments to protect the healthcare worker from airborne and aerosolized bloodborne pathogens.

Methodology

The Bacterial Filtration Efficiency test will be analyzed as to the particle size distribution of its spray. The size distribution (which is the primary parameter affecting aerosol penetration) will be measured for several liquids, with and without different bacteria. The sprays will be size measured upon generation and after mixing with dry air when only the residues are left. The size-dependent penetration of inert and biologically active test aerosols will be compared with each other. New

bacterial testing methods will be studied which can detect bacteria directly.

Significant Findings

None to date.

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 face seals 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 face seal 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. Face seal leak sites will be identified by observation of fluorescence of the aerosol deposited at the site(s) when illuminated by ultraviolet light. The one-dimensional width of observed leaks will be measured and their location categorized by facial location. Anthropometric facial dimensions of the subjects will also be measured. The fifth objective will be accomplished by performing the same tests on a mannequin fitted with a respirator using a breathing simulator. Data will be analyzed by conditional logistic regression, multiple linear regression and ANOVA.

Significant Findings

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 commencement of tests on human subjects.

Tinopol CBS-X was selected as the test agent in this study. This compound is water soluble, non-mutagenic, non-carcinogenic, and of low toxicity. It also has a much higher fluorescent efficiency than the coumarin-type used in our previous studies, and is expected to provide better definition of leak sites. An aerosol generating and exposure system including three Liu nebulizers, aerosol conditioning system and exposure chamber (Air Techniques System, Model TDA-71, 2.5 m³ chamber with air lock) has 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/m³. Testing human subjects has commenced and it is about 50% complete.

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Adsorption of Vapor Mixtures onto Activated Carbon

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Program Area: *Respirator Research*
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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. Breakthrough curves for p-xylene alone and paired with o-dichlorobenzene and p-dichlorobenzene have been conducted. The data indicate that the kinetic adsorption capacity for p-xylene is reduced in proportion to its lower concentration when paired with the different dichlorobenzene isomers. The rate constants however have remained unchanged.

Additional breakthrough curves using different vapor pairings are currently being conducted.

Aerosol Penetration Behavior of Respirator Valves

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Program Area: *Respirator Research*

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Funding Level: *\$18,102 (\$18,102 Cum)*

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 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 workrates will be evaluated.

The survey of respirator users has been prepared and is presently being distributed and completed by thirty local companies. As part of this survey, we will identify companies willing to supply used valves and visit their sites to evaluate work practices. These companies will be given new valves, which will be used for some period of time before evaluation of particle size penetration in the laboratory.

Significant Findings

None to date.

Lighter Compact Respirators for Toxic Vapor Protection

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Program Area: *Respirator Research*

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Importance to Occupational Safety and Health

The successful development of smaller, lighter and more dependable respirators offer significant

opportunities for improved safety for workers who may be exposed to hazardous gases in the commercial work place. More compact and reduced weight respirators will receive greater use and acceptance by workers who, as is well known, may find the respirators a hindrance and inconvenience. Furthermore, the respirators under investigation are expected to give longer life and potential reusability by use of selected polymers as absorbants rather than activated charcoal. Activated charcoal is found to degrade substantially in the presence of water vapor and other interferants.

Objectives

It is a primary goal of the research to demonstrate that oscillatory flow through the absorbent filter material can very substantially increase the breakthrough times and may in fact allow unlimited time of use for vapors of moderate toxicity. Preliminary analyses at Dynaflo, Inc. have shown that oscillatory flow through adsorbent passages can indefinitely reduce the incoming toxic gas concentration to levels of one or two percent of the ambient concentrations. Use of specially selected polymers as absorbents are expected to allow considerably greater reductions in the breathed vapor concentrations.

Methodology

The research is divided into analytical and experimental parts. To guide the experimental choice of geometries flow rates and polymer characteristics, a Fortran 77 code is being developed to simulate the mass transfer occurring in the polymer passages during oscillatory flow. The experimental program involves first the measurement of partition coefficients for polymer/gas pairs of interest followed by oscillatory flow tests of a small filter module to prove the feasibility of the filter concept. A simulated toxic gas generator will supply low gas concentrations for the test units and concentrations will be measured using a flame ionization detector.

Significant Findings

None to date.

Effects of 27 MHz Radiation on Somatic and Germ Cells

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Program Area: *Other Occupational Needs*

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Importance to Occupational Safety and Health

Workers are routinely exposed to 27-MHz and other frequencies of electromagnetic radiation. Current health protection guidelines are based upon the premise that adverse health effects are due to tissue heating. It is of primary importance for occupational safety and health to determine the validity of this premise. To this end studies are being conducted of the effects of continuous wave (CW) and pulse-modulated (PM) 27-MHz and 2450-MHz RF electromagnetic radiation on mammalian cells *in vitro*.

Studies conducted to date provide firm evidence that these RF radiation frequencies affect cell mitotic activity under conditions that simulate occupational exposure. 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.

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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 ($37 \pm 0.2^\circ\text{C}$) 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/G₁ phase.

A statistically significant reduction in the ability of mouse spermatozoa to fertilize mouse ova occurred following a 1 h exposure of sperm at $37 \pm 0.2^\circ\text{C}$. 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.

The effects of CW 27- or 2450-MHz RF radiation on stress protein induction in CHO and HeLa cells was investigated by exposing cells for 2h at SARs of 25- or 100 W/kg under isothermal ($37 \pm 0.2^\circ\text{C}$) condition. Stress proteins were assayed by acrylamide gel electrophoresis. Characteristic stress protein responses were detected in positive control CHO cells exposed to heat stress (40°C , 2h) or Cd++ ($45 \mu\text{M}$). No stress proteins were detected in RF exposed cultures.

Two factor studies were undertaken to investigate the effects of interactions of RF radiation with other agents. Glioma were exposed or sham-exposed for 2h to CW 27- or 2450-MHz RF radiation under two conditions: (1) in the presence of 20% deuterium oxide (D₂O), or (2) at 39°C . RF exposure at 25 W/kg, in the presence of D₂O, resulted in a statistically significant suppression of cell proliferation in direct contrast to the stimulatory effect of RF exposure at this SAR in the absence in D₂O-free medium. Temperature elevation (2°C) during RF exposure had the opposite effect. RF exposure at 39°C resulted in statistically significant enhancement of cell proliferation compared to glioma sham-exposed at this same temperature. These results indicated RF interactions.

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.

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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 $1 \mu\text{M}$ 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 bromo-cresol 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 bromocresol 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 $[^3\text{H}]\text{-NaBH}_4$ 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 ^3H -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 fraction) 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.

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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 ³²P 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 ($r=0.35$, $n=46$), and DNA adducts ($r=0.33$, $n=47$). Likewise, levels of styrene in the exhaled air and blood and styrene glycol in the blood were all significantly correlated with each other. However, 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.

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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 ongoing 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 are being 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.

An exposure index to hydrocarbons is being calculated and will be used in a univariate and multivariate statistical analysis of risk factors for chronic renal disease. The univariate analysis will employ the odds ratio and multivariate analysis will employ Cox's Linear Logistic Regression Model.

The statistical minimum number of total cases and controls is 300 of each. To date, 330 cases and 307 controls have been interviewed. The original three year study began on September 15, 1989 and has been extended until September 15, 1993.

Significant Findings

None to date.

Permeation of Glove Materials by Organic Solids

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Importance to Occupational Safety and Health

The exposure of unprotected hands to solid organic chemicals can result in various injuries via dermal absorption. Common protective glove

materials may allow chemicals to permeate, creating conditions hazardous to human health. To provide optimum protection, methodology must be developed to evaluate the critical permeation characteristics of breakthrough time (BT) and steady-state permeation rates (SSPR). By evaluating a representative set of chemicals, glove materials, and exposure conditions, it should be possible to determine what effect chemical vapor pressure and relative glove/permeant solubility have on BT and SSPR. Further, the availability of this information will aid in selection of optimum gloves and lead to improved glove materials.

Objectives

The development and validation of a method for evaluation of permeation behavior of 5 protective glove materials when exposed to 13 solid organic chemicals was the initial objective of the study. Current investigations include the effect of temperature, relative glove/permeant solubility, vapor phase transfer, and using saline as a collecting medium to simulate actual usage.

Methodology

A stainless steel permeation cell has been designed that allows an organic solid (in pellet form) to rapidly be brought in contact with a test membrane. By including a long sample introduction neck, it is also possible to conduct vapor phase permeation studies with known diffusion paths. A helium stream is passed across the opposite membrane face which then flows through a sampling loop of a 10-port valve and finally to an FID detector. By changing the position of the valve, the contents of the sampling loop can be directly injected onto a GC column for analysis. This overall

arrangement allows for the rapid and automated determination of glove permeation characteristics. The cell to detector transfer line is maintained at 250°C to minimize condensation of any collected permeants. The GC analysis at the end of each exposure not only permits calculation of SSPR values but would indicate if any significant decomposition was occurring. Using this method, 5 common glove materials have been evaluated for their permeation characteristics against 9 test permeants. For studies involving saline as a collecting medium, the solution was passed through the "gas" side of the cell at a rate of 10 ml/min and split at 5 minute intervals. Each split was then extracted, concentrated, and then quantified by GC/MS.

Significant Findings

Since the last report period, studies have been conducted to see what role direct contact plays on permeation. Pellets of either phenol or dichlorobenzene were placed 1 cm from the membrane face and the BT and SSPR were determined. SSPR values typically were slightly higher for vapor phase contact. This can be attributed to the fact that each membrane exhibited bowing due to the lack of support normally provided by the pellet. Overall, significant increases in BT were observed well beyond the time required to achieve the equilibrium vapor pressure at the exposed membrane face (Table). For phenol vs. neoprene and p-dichlorobenzene vs. polyurethane, the experiment was repeated at various exposure distances to determine if the effect was due to variations in concentration or in the time required to saturate the vapor phase. It was observed that breakthrough times remained relatively constant regardless of the distance used.

Table: BT Comparison for Direct Contact and Vapor Phase Transfer.

	Distance	Phenol Direct	Phenol Vapor	p-dcb Direct	p-dcb Vapor
Latex	1 cm	10.4	19.5	5.2	8.0
PVC	1 cm	10.6	15.0	5.2	5.8
Nitril	1 cm	185	320	ND	ND
Urethane	1 cm			3.6	10.5
	2 cm				11.7
Neoprene	3 cm				12.0
	1 cm				
	2 cm				
	3 cm				
ND = Not detected. All materials at 5 mil thickness. BT in minutes. Single point determinations.					

Glove/permeant solubility was then determined using the method described. The study was conducted by placing a weighed section of membrane in direct contact with a solid pellet in a sealed glass container. Each container was stored at 22°C for a period of two weeks at which time each section was reweighed. BT values showed little correlation to the vp, solubility and SSPR. Current work involves determination of BT and SSPR values for each glove/permeant pair where a saline solution is used as the collecting medium rather than helium. To date, two permeants (phenol and p-dichlorobenzene) have been evaluated versus latex. These two materials both show high permeation rates and rapid breakthrough for latex and represent both a hydrophobic and hydrophilic species. For p-dichlorobenzene, breakthrough occurred in the 5–10 minute sample and an SSPR of 0.88 mg/min/cm² was observed. For phenol, breakthrough occurred in the 15–20 minute sample and 19.20 mg/min/cm² respectively. BT values were consistent with those observed for gas collection where significant variations in the SSPR were measured. In the case of p-dichlorobenzene, using saline resulted in SSPR values of ~10% in those obtained with He as the collecting medium. Phenol SSPR were about 10 times larger.

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Selective Real-Time Detection of Olefin Gases and Vapors

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Importance to Occupational Safety and Health

This project focuses on measuring 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 microsensor-based instrument will permit collection of more accurate exposure data for the target gases and vapors.

Objectives

The goal of this research has been to develop microsensor-based instrumentation for selective real-time measurement of several olefin and diene gases and vapors in the presence of common olefin and non-olefin industrial co-contaminants. The primary focus has been on the detection of styrene, ethyl acrylate, vinyl acetate, acrylonitrile, 1,3-butadiene, vinyl chloride, and b-chloroprene. Response data for other olefins have also been collected. The instrument employs a surface-acoustic-wave (SAW) sensor as the detection element. Selectivity for a given target olefin can be achieved by coating the sensor surface with one of several regenerable trapping reagents.

Methodology

Several trapping reagents have been synthesized and tested as sensor coatings for detection of each of the target analytes. The reagents comprise platinum-olefin coordination compounds of the

general formula $\text{trans-PtCl}_2(\text{amine})(\text{olefin})$ designed to react, via substitution of the initially bound olefin, with certain olefin(s) and dienes. Changes in the electronic and steric properties of the ligands in the reagent allow for adjustment of the sensor sensitivity and selectivity. The SAW sensor has been incorporated into a compact prototype instrument.

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 $\text{trans-PtCl}_2(\text{ethylene})(\text{pyridine})$ and poly(isobutylene). In all cases post-exposure regeneration of the reagent is possible by treatment with ethylene, *in situ*. Selectivity for the target olefins in the presence of other olefin gases and vapors has been achieved and is attributed to steric and electronic factors favoring the target olefins. A systematic investigation of steric factors affecting the olefin-substitution reactions has shown that a remarkably high degree of selectivity is found for unhindered olefins. For example, ethyl acrylate can be monitored without interference from its more hindered isomers methylmethacrylate and methylcrotonate. Similarly, the response to styrene is about 8–10 times higher than that for α -methylstyrene and indene. Testing of various butene isomers shows that 1-butene can 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 $\text{trans-PtCl}_2(\text{ethylene})(\text{pyridine})$ complex. However, use of the related reagent $\text{PtCl}_2(1\text{-hexene})(\text{pyridine})$ coated on a 30-MHz SAW device permits 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 $[\text{PtCl}_2(\text{pyridine})]_2(\text{butadiene})$, which effectively amplifies the sensor response. No interference is seen from several industrially relevant non-olefin gases and vapors, and repeated regeneration of the reagent is possible by brief exposure to 1-hexene. Certain olefins can also be measured with this reagent, but only at concentrations higher than that of butadiene. For example, acrylonitrile can be measured above 2 ppm using the 1-hexene complex whereas it cannot be measured using the corresponding ethylene complex. Chloroprene can also be measured but only at concentrations above 100 ppm. Vinyl chloride gives responses above

about 30 ppm. Vinylidene chloride, dichloroethylene and trichloroethylene neither react nor interfere with the responses of the other analytes. Replacing pyridine by 2,6-dimethylpyridine in the 1-hexene complex precludes reaction by styrene but still allows sensitive detection of acrylonitrile and butadiene. Use of a 60-MHz sensor instead of a 30-MHz sensor increases the sensitivity to these analytes by a factor of four (e.g., the LOD for butadiene is 24 ppb). Interestingly, ethyl acrylate does not react with the 1-hexene complex whereas it reacts quite rapidly with the ethylene complex. Thus, it is 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. Laboratory testing of the instrument is currently being completed.

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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. After laboratory optimization and performance evaluation of the device, it 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 biological activities of vapor and condensed phase isocyanate.

Objectives

This project will entail a critical laboratory comparison of the methoxy-phenylpiperazine (MOPIP), methymino-methylanthracene (MAMA), and tryptamine (TRYP) methods for TRIG in terms of selectivity, sensitivity, accuracy, and precision of analysis, 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 levels and physical state in representative workplace atmospheres, including isocyanate manufacturing and flexible polyurethane foam production.

Methodology

Analytical derivatives of thirteen isocyanate compounds with MAMA, MOPIP, and TRYP were synthesized in the laboratory. The isocyanates included methylisocyanate, butyl-isocyanate, phenylisocyanate, benzylisocyanate, o-tolylisocyanate, p-tolylisocyanate, 1,6-hexamethylenediisocyanate (HDI), 1,6-hexamethylenediisocyanate-biuret (HDI-BU), 2,4-toluenediisocyanate (2,4-TDI), 2,6-toluenediisocyanate (2,6-TDI), methylene-bis-(4,4'-cyclohexylisocyanate) (HMDI), methylene-bis-(4,4'-phenylisocyanate) (MDI), and polymethylene-polyphenyl-isocyanate (PMPPPI). After synthesis and purification, the identities of the derivatives were confirmed with elemental analysis and infrared spectroscopy, and where needed, NMR and mass-spectroscopy.

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. For each of the derivatizing agent groups, analytical response was examined with 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.

Preliminary work on the dichotomous sampler for TRIG aerosol and vapor was also begun. The dichotomous sampler consisted of an annular diffusional denuder (University Research Glassware) in series with a treated filter, both of which were coated with 4-nitrobenzyl-n-propyl-amine (Nitro Reagent) derivatizing agent for isocyanates. Sampling of a test atmosphere of vapor and condensation aerosol of MDI was accomplished with the sampler.

Significant Findings

Preliminary analysis of the data indicates significant intra-group differences across isocyanates for each of the three derivatizing agents and their

three associated detection modes. For equal weighting of response factors across isocyanates, the variabilities as measured by relative standard deviations of the means were as follows: MAMA derivatives; fluorescence, 66%; UV at 245 nm, 34%; UV at 370 nm, 38%; for MOPIP derivatives – electrochemical, 25%; UV at 242 nm, 78%; UV at 277 nm, 38%; for TRYP derivatives – electrochemical, 55%; fluorescence, 38%; UV at 280 nm, 37%.

The ratios of response factors across detectors exhibiting least variability among the isocyanates were the ratio of fluorescence to UV absorbance for TRYP derivatives with a mean of 2.4 and RSD of 17.6%, and the ratio of UV absorbencies at 370 and 245 nm for MAMA derivatives, with a mean of 0.09 and RSD of 31.1%. However the latter was extraordinarily consistent across isocyanates except for PMPPI. Without PMPPI, the mean ratio was 0.09 with a RSD of only 7.7%. These results indicate promise for reliable identification of TRIG of unknown origin; however quantitation will be more difficult due to the wide variation in response factors across isocyanates. For the initial work on the dichotomous samplers, the overall recovery efficiency for MDI was 97.6% (s.d.= 6.6%) for a test atmosphere of 33.1 ppb. On average, the denuder collected an amount of MDI equal to 9.8 ppb (RSD = 12%); the remainder of the MDI was found on the back-up filter. In comparison, the expected concentration of MDI vapor based on its vapor pressure at the experimental temperature was approximately 9 ppb. This preliminary data gives a clear indication that the dichotomous sampler was efficiently separating vapor and condensed phase MDI.

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. 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" concept using fixed beam (criterion for use of open path monitoring system results for real time decisions of level of respiratory protection).
5. Field testing of fixed beam open path-gamma concept.
6. Design of system for rapid beam movement.

Methodology

We have designed and received a small, transportable OP-FTIR system specifically for use in the workplace or in environmental applications where portability is a significant consideration. An experimental chamber was modified and validated for the evaluation of the OP-FTIR. New methods and software to implement those methods were developed to identify unknown contaminants in workplace air and to compensate for air contaminants in "clean" background air. 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.

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, Chicago, IL.
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 open path-FTIR system in cases in which there is no source of clean air with which to obtain a useful background spectrum.

Publications

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Company Characteristics and Medical Screening of Workers

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Program Area: *Other Occupational Needs*

Grant Number: *1 R01 OH02739-01*

Start & End Dates: *09/01/90 - 08/31/92*

Funding Level: *\$48,535 (\$48,535 Cum)*

Importance to Occupational Safety and Health

Workplace characteristics like wages, unionization, turnover, and firm size do not directly influence worker health but can affect the value to employers of medical screening. Employers may choose whether to screen to maximize the benefits to them. However, such a decision may not be beneficial to the health of the screened workers and may largely shift the costs of illness to the workers or other employers, thus reducing the incentive to reduce workplace hazards.

Objectives

The long-term objective of this research is to identify the extent of excessive medical screening, so that, if needed, appropriate public policies can be designed.

Methodology

The proposed research uses data from two national studies that provide information on potential exposure to workplace hazards, the prevalence of several types of medical screening, unionization, firm size, and turnover (the NOHS and NOES), as well as industry-specific data on wages and turnover. Logistic regression analysis will be employed to estimate the association of wages, unionization, turnover, and firm size with the prevalence of medical screening, controlling for workplace occupational health risks.

Significant Findings

1. Economic variables, like unionization, turnover, wages, and plant size have substantial impacts on the prevalence of workplace medical testing, including preemployment medical examinations and periodic ophthalmologic examinations,

- audiometric examinations, blood tests, urine tests, pulmonary function tests, and xrays.
2. Exposure to hazards, as measured by the NOHS and NOES surveys, was only infrequently related to the prevalence of workplace medical screening. We cannot determine whether this finding reflects an actual weak relationship or inadequacies in the NOES/NOHS survey data.
 3. The prevalence of workplace medical screening rose substantially between the 1972-1974 NOHS survey and the 1981-1983 NOES survey. This increase is almost entirely attributable to changes in the economic benefits of screening. If anything, changes between the two surveys not captured by our economic data would have reduced the prevalence of ophthalmologic exams, xray exams, and preemployment exams.

Publications

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Minimizing Work Schedule Disruption with Bright Light

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Start & End Dates: *05/01/92 - 04/30/94*
Funding Level: *\$153,663 (\$153,663 Cum)*

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

This project began in May, 1992. Following acquisition of supplies and equipment required for the study, recruitment efforts were implemented and studies have progressed in a timely manner. Since data acquisition is ongoing, no findings were available at the time of this report.

Measurement of Alkenyl/Epoxy DNA Adducts by GC-MS

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Grant Number: 5 R01 OH02792-02

Start & End Dates: 01/01/91 - 12/31/93

Funding Level: \$134,173 (\$264,940 Cum)

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 pentafluorobenzoylation) 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 Q⁶-G ethylene oxide adduct. A novel chemical transformation reaction was required for this adduct that would retain the Q⁶-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 Q⁶-G ethylene oxide adducts.

Publications

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Assessment of Occupational Exposure to Aflatoxin

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Start & End Dates: *05/01/91 - 10/31/92*

Funding Level: *\$192,394 (\$192,394 Cum)*

Importance to Occupational Safety and Health

Available epidemiologic studies from around the world provide evidence for association between the incidence of lung and other cancers and past exposure to aflatoxins in contaminated grain dust. In the United States, limited exposure data are currently available to assess the potential risk of lung cancer among farmers and agricultural workers due to inhalation of aflatoxin contaminated grain dust.

Past analysis of grain dust samples from the midwest and southeast corn growing belt has demonstrated the presence of aflatoxins in high volume samples of airborne dust. Recent drought conditions have led to flourishing fungal growth and consequent production of some alarming levels of aflatoxins in the corn crop. Our preliminary study indicates once detected, aflatoxin B₁ in airborne dust samples collected during harvesting, continues throughout grain unloading and animal feeding. The possibility for repeated hot and humid seasons creates a growing need to define the possible role of aflatoxins in the etiology of lung and other cancers.

Objectives

The long-term goal of this proposal is to determine the average yearly exposure of farmers to aflatoxin B₁ in airborne grain dust from repeated low level exposures during various on-farm grain handling activities. This goal creates the need for an efficient, more sensitive, and highly specific analytical method for the determination of low levels of aflatoxins in airborne grain dust samples. Therefore, the specific objectives of this proposal are:

1. To develop and validate a one-step extraction and analysis technique for the separation and quantitative determination of aflatoxin B₁ in airborne grain dust samples.
2. To collect and analyze statistically acceptable dust samples in a cross-sectional survey representative of regional on-farm agricultural grain handling operations.
3. To determine the proportion of aflatoxins in respirable dust particles and the effect of high and low seasonal temperature, rainfall or humidity, and grain handling on the aflatoxin content in bulk corn and dust samples.
4. To identify and quantify other natural toxins such as ochratoxin, zearalenone, vomitoxin, and fumonisin, which may be detectable during the course of aflatoxins analysis in grain and grain dust.

Methodology

The analytical methods are based on the application of supercritical fluid extraction of grain dust samples, followed by on-line analysis by SFC or HPLC/MS. Airborne dust samples are directly extracted with supercritical carbon dioxide using an SFE apparatus, in the presence of small amounts of organic solvents as fluid modifiers, followed by off-line analysis of the extract. Off-line and on-line supercritical fluid extraction methods have been developed for analysis of aflatoxin, and other mycotoxins in grain dust samples. Funding of the above proposed research plan was limited to the laboratory method development only. Anticipated future field sampling will include on-farm grain handling operations in Iowa and three other states with high potential for aflatoxin contamination in grain (e.g. GA, OH, and OK). The proposed field study is pending revision and resubmission.

Significant Findings

Since the beginning of the currently funded method development phase on July 1, 1991, the SFE procedure for aflatoxin has been optimized, leading to a lower detection limit of 1 ng per sample. A new

SFE method was also developed and optimized for the detection of fumonisins in grain dust. Both the aflatoxin and fumonisin methods were first developed as off-line extractions with SFE followed by HPLC analysis. SFE analysis of aflatoxin B₁ has been optimized on-line with HPLC/MS. However, greater sensitivities were obtained with on-line SFE/HPLC with fluorescence detection. Further improvement in mass spectrometric detection for aflatoxin B₁ requires derivatization followed by negative chemical ionization, which has been attempted but requires further development. A multi-toxin screening method has been developed for on-line analysis of the SFE extracts using HPLC/MS. These methods are being evaluated using field samples from the 1992 harvest season.

Publications

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Dosimetry for Workplace EMFs at Power-Line Frequencies

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Grant Number: *1 R01 OH02945-01*
Start & End Dates: *05/01/92 - 04/30/94*
Funding Level: *\$118,188 (\$118,188 Cum)*

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

During the first six months of the project the work has proceeded along the following lines:

1. We have surveyed the magnitudes of the power-frequency magnetic fields in our machine shop and, to our surprise, found these magnetic fields to be extremely low, generally less than 1 μ T for grounded and shielded power tools such as the power drill, band saw, etc. For other relatively unshielded power tools such as sanders and grinders, the magnetic fields were considerably higher and on the order of 7-15 μ T. However, the magnetic fields decreased rapidly and were substantially lower at the locations of the operators for these latter machine tools.
2. Magnetic fields have been measured in proximity to the hand drills and have been found to be as high as 500 μ T, though reducing rapidly with distance away from the handle of the drill. We have been able to express the measured three-dimensional variations of the vector magnetic fields as though they were created by three equivalent orthogonal loops of different parameters $N I r^2$ that are products of currents I , squares of radii r^2 , and number of turns N . The three-dimensional magnetic fields thus represented have been used to calculate the

induced currents in a 1.31-cm resolution anatomically based model of the human body with a nonextended arm used to date. Some of the highest section-averaged current densities occur for the region of the torso, approximately 100–120 cm above the feet. The highest section-averaged current densities are calculated to be about 20–25 $\mu\text{A}/\text{m}^2$.

We are presently proceeding to measure and characterize the equivalent loops of values NI^2 that may be used to describe the magnetic fields of other industrially relevant sources, such as hand saws, motors, fluorescent desk lamps, etc., and use this information to calculate induced current densities and internal electric fields in the models of the human body representing realistic postures, including extended arm, etc.

3. We have also fabricated prototype contact-current and stored-energy meters for specifications of 0–50 mA for the contact-current meter, and a similar current rating and 0–15 kV open-circuit-voltage rating for the stored-energy meter, respectively. These meters are presently undergoing calibration testing before being taken into the occupational settings for field testing.

Significant Findings

None to date.

Permeation Mechanisms of Pesticides Through Materials

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Program Area: *Other Occupational Needs*

Grant Number: *1 R01 OH02951-01*

Start & End Dates: *09/30/92 – 09/29/94*

Funding Level: *\$117,631 (\$117,631 Cum)*

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 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; 0.41–1.37 mg/cm²/min) and penetrates Latex (causes holes within minutes). The permeation is enhanced by the presence of xylene inert component.

Safety, Industrial Relations, and Productivity

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Program Area: *Other Occupational Needs*
Grant Number: *5 K01 OH00075-03*
Start & End Dates: *09/30/88 – 09/29/92*
Funding Level: *\$32,383 (\$97,183 Cum)*

Importance to Occupational Safety and Health

This study will help assess the likely impact of "right-to-know" and other worker-oriented policy strategies in occupational safety and health. Using a wide range of statistical data from the 1980s, it will measure worker, labor union, and management responses to perceived workplace hazards. Particular emphasis will be placed on worker turnover, the incidence and outcome of union representation elections, and labor productivity in manufacturing and construction. Hazard-related industrial conflict is one of the most important yet least understood social consequences of unsafe and unhealthy working conditions.

Objectives

This study examines worker, labor union, and management responses to occupational safety hazards in order to measure the association between working conditions, industrial relations, and labor productivity. Research to date, based on data from the 1970s, suggests that hazardous working conditions exert significant negative influences on the quality of industrial relations, which in turn reduces labor productivity and economic performance. This study will update and expand the existing literature using a broad range of statistical data sources covering the 1980s.

Methodology

The study will use seven different data sets to examine a number of worker, union, and management responses to occupational hazards. Information on working conditions will be obtained from Bureau of Labor Statistics and Workers' Compensation records and merged with the seven data sets using industry and occupation codes. Outcome variables will include worker quits and desire for union representation, union success in representation elections, management strategies to counter union organization, and measures of productivity in construction and manufacturing industries. Multivariate statistical methods will be used to isolate the independent influence of working conditions *per se* from other important determinants of these outcome variables.

Significant Findings

High risks of occupational injury and illness lead to worsened industrial relations and lower worker productivity in manufacturing industries. Comprehensive input and output data on 450 manufacturing industries for 1959 through 1978 were analyzed. Labor productivity was measured in terms of value added per production worker hour, after controlling for capital, materials, and energy per worker. Compared to industries with lower occupational injury rates, productivity in industries with high injury rates was 1% lower in 1959, 4% lower in 1963, 3% lower in 1968, 6% lower in 1973, and 12% lower in 1978.

Worker survey data from the University of Michigan's Panel Study of Income Dynamics were analyzed to identify the influence of occupational hazards on strike rates. For 1976–78, strike rates were 67% higher in industries with high occupational injury rates than in industries with low injury rates. For 1985–87, strike rates were 39% higher in more hazardous industries compared to less hazardous industries. These analyses controlled for other determinants of strike probabilities, such as worker demographic characteristics, skill levels, and geographical location.

Microsensor Array for the Identification of Organic Vapors

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Start & End Dates: *07/15/89 - 03/14/93*

Funding Level: *\$27,251 (\$90,878 Cum)*

Importance to Occupational Safety and Health

Currently available portable direct-reading instruments for organic vapors generally lack the selectivity necessary to identify a given vapor or to discriminate between the components of even simple vapor mixtures. The successful project will yield an array of surface-acoustic-wave (SAW) sensors capable of identifying organic vapors from several classes and differentiating between components of vapor mixtures. The small size and low power requirements of the array will facilitate incorporation into miniaturized instrumentation suitable for real-time personal monitoring applications.

Objectives

Arrays of coated-SAW microsensors can be developed for the measurement of organic vapors. Pattern recognition analyses of the multidimensional sensor response data can be used to determine the identity and quantity of each target vapor.

Methodology

Responses to several members of each of 11 classes of organic vapors are being tested using a series of chemically sensitive SAW-sensor coatings. The sensor responses are then analyzed collectively using pattern recognition methods. Subsets of coatings can then be chosen based on their ability to discriminate between different types of organic vapors. Coating materials consist of various polymers with differential absorption affinities for organic vapors. Exposure of the sensors to industrially relevant vapor mixtures is being performed to verify the results predicted from the pattern recognition analyses. Sensor response models

are being developed to optimize the coating selection for a given exposure situation and to predict the importance of potential interferences.

Significant Findings

Test results with 17 coating materials indicate that with a simple four-sensor array discrimination of vapors from 11 different chemical classes can be readily achieved in most cases and discrimination of vapors within the same class is possible in several cases. Application of the pattern recognition method referred to as extended disjoint principal component analysis (EDPCR) has facilitated the selection of optimal coatings for use with a given set of potential air contaminants. The method appears to be quite general and to have advantages over conventional cluster analysis methods for this purpose. It can be used to predict the performance of an array for a given potential exposure situation. For example, using responses from a representative subset of individual vapors, including benzene, xylene, trichloroethylene, carbon tetrachloride, hexane and isooctane, EDPCR indicates that all vapors can be identified and 96% of the binary mixtures of these vapors can be correctly identified and discriminated using a set of four polymer coatings that cover a range of polarity and solubility properties. An error model has been incorporated into this approach to account for temperature and humidity variations that may affect the accuracy of the predicted results. Experimental verification of these modeled results is nearly complete.

Additional analyses have focused on the development of semi-empirical sensor response models based on vapor boiling point, vapor/coating solubility parameters, and vapor/coating solvation parameters. As part of this effort, it has been shown that the SAW sensor can be used for determining the solubility parameters and solvation parameters of any coating. This is normally performed by gas chromatography. Use of the sensors to obtain such information has several potential advantages, including simplicity of sample preparation and analysis, room temperature or high-temperature operation, compensation for humidity and substrate effects, and simultaneous testing of several coatings.

Each of the three models has been used to develop regression equations from which modeled response values are derived. For the boiling point model, correlations between experimental and modeled responses were highest for the non-polar coatings and results for all coatings agree remarkably well with theoretical predictions assuming ideal vapor behavior. This model can be used to estimate the relative responses of a set of vapors on a given coating. The solubility parameter model yields improved accuracy over the boiling point model.

Best results were obtained with the more complex model based on solvation parameters, with modelled sensor responses values falling within 60% of experimental values for all of the vapors and coatings. With this model, array response patterns can be modeled very accurately and the performance of the array for any number of vapor exposure scenarios can be determined apriori. Results demonstrate the ability to determine the responses to untested target vapors, the expected discrimination between mixtures of target vapors, and the importance of potentially interfering vapors for a given set of coated sensors in the array. The effect of humidity on the responses to a representative set of organic vapors has been characterized and in most cases is not significant. Limits of detection for many of the vapors tested are below their respective ACGIH-TLV values. However, this is not the case for several of the more volatile vapors. Incorporation of a sample preconcentrator into the test system will yield sub-TLV detection limits for all vapors.

Publications

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Optical Remote Sensing and Computed Tomography in Industrial Hygiene

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Grant Number: *5 K01 OH00103-02*
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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 in 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. 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. The result of this research will be the development of an operating system for measuring gas and vapor concentration distributions that is non-invasive and operates in real-time.

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, 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 four configurations have been evaluated 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.

An infrared optical remote sensing device is

being evaluated for use in the chamber studies using a tracer gas.

Publications

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

- 1-3. 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
4. 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
5. 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.

Maximum likelihood methods in this setting can be computationally intensive and complex. Thus, one-step approximate methods will be proposed, investigated, and used whenever possible.

Significant Findings

A presentation entitled "Correcting Point and Interval Estimates of Symptom Prevalence Ratios for Exposure Measurement Error: The ACE Study" was prepared. This was presented on Tuesday, September 22, 1992 at the very well attended Workshop on Epidemiologic Methods which preceded the international symposium "Epidemiology in Occupational Health" organized by NIOSH and held in Cincinnati, Ohio. The presentation reviewed basic methods for correction of point and interval estimates of relative risk, and illustrated the use of these by correcting point and interval estimates of symptom prevalence ratios found among the ACE pharmacists. The exposure variable considered in this analysis was number of days per week that antineoplastics were mixed. There were 738 pharmacists for whom data on this exposure variable, which we will denote as Z, were available. The validation study contained data on 73 pharmacists who completed a daily log of all antineoplastic drug mixing activities for one week. The number of days per week antineoplastics were mixed was rederived from these data, and for the purposes of this analysis is considered the "true" exposure variable, which will denote by X. The correlation between X and Z was calculated at 31%, indicating that a study based upon measurements of Z is only 10% as powerful as a study based upon measurements of X. Without adjusting for measurement error, we concluded that it is unlikely that any exposure-disease relationship existing in these data would be detectable except with extremely large sample sizes.

We then used the method given by Rosner et al. to explicitly correct the point and interval estimates of relative risk for bias due to exposure measurement error. We estimated the parameters for the exposure measurement error model, $X = 1.33 + 0.133 \cdot \text{SEX} + 0.401 \cdot Z$. We then calculated the uncorrected and corrected point and interval estimates of prevalence odds ratio (POR) for acute neurological symptoms and obtained the following results:

Acute Neurological Symptoms		
	uncorrected POR (95% confidence interval)	corrected POR (95% confidence interval)
Mixing antineoplastics (days/week) (2 day/week increase)	1.26 (0.94, 1.69)	2.76 (0.77, 9.91)
Sex (Female=1/Male=0)	1.83 (1.26, 2.65)	1.91 (1.31, 2.77)

The estimate of the effect of exposure increased nearly threefold, and the 95% confidence intervals widened considerably, reflecting the true uncertainty in the data resulting from both sampling variability and exposure measurement error. Since gender was associated with exposure in these data, the estimate of the gender effect is also changed somewhat by the measurement error correction procedure. The Rosner et al. method makes several assumptions which are not satisfied by the present data set: (1) it requires a "rare disease", where here the prevalence of neurological symptoms is 33%; (2) it requires that the distribution of $X|Z$ is normal, while here the conditional distribution exhibits a right-skewed shape that is not likely to follow a normal distribution.

Current work involves investigating parametric full maximum likelihood methods for a constant prevalence ratio model with a more 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 lead to a closed form likelihood for the main study distribution of symptom prevalence conditional on exposure. Semi-parametric models are also being considered.

TCD as a Screening Procedure for Exposures to Toxicants

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Grant Number: *5 R03 OH02932-02*

Start & End Dates: *09/30/91 – 09/29/93*

Funding Level: *\$16,005 (\$32,512 Cum)*

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 pCO₂ 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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Funding Level: *\$19,363 (\$19,363 Cum)*

Importance to Occupational Safety and Health

Dose-response assessment is used as a criterion in establishing causality from associations observed in epidemiologic studies. It is also used to improve the understanding of biologic mechanisms and as a basis for setting exposure standards in occupational and environmental settings. For this project, we will examine two sources of bias that may alter dose-response relationships. In particular, we will describe possible distortion of dose-response curves due to competing risks that are related to dose and to the choice of referents for cohort mortality studies. Results from this project may then be used to increase the sensitivity of future 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 quantify two biases that may alter dose-response relationships in occupational epidemiology studies. The first is from competing risks that may be exposure-related. The second is from the choice of referent population or weights applied to the different age groups.

Methodology

To examine competing risks as they contribute to the healthy worker survivor effect, we will fit Poisson regression models to several data sets and separately assess the contribution of exposure-related morbidity and mortality from causes other than the one of interest in influencing the shape of the dose-response curve.

Significant Findings

None to date.

A Volatile Aerosol Sampler and Particle Size Analyzer

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Start & End Dates: *09/30/92 – 09/29/93*
Funding Level: *\$22,495 (\$22,495 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.

Objectives

The first goal of this work is to develop a prototype Vapor/Particle Sampler (VPS) for anisokinetic separation of the airborne VOC containing particles and coexisting vapor into two identifiable fractions according to their differential inertia. Our second goal is to develop a prototype Multiple Vapor/Particle Sample (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, 3.5, 5, 10 and 20 μm aerodynamic diameters, where, 3.5 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 will be 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.

The performance of the sampler will be tested using laboratory-generated vapors and aerosols. Monodisperse uranine-tagged oleic acid aerosols of known size and concentration generated by a Vibrating Orifice Aerosol Generator will be used for calibration of the VPS and MVPS samplers. The mass concentrations of oleic-uranine particles will be quantitatively analyzed by fluorometry. The polydisperse particle samples will be generated from vegetable oil by a Collison nebulizer. The sampling efficiencies will be measured at various inlet flow rates and various ratios of the dichotomous flow rates. The vapor collection efficiency of the VPS sampler will be tested in a chamber equipped with a vapor generating device. Sampler performance will be compared to other well-established reference samplers.

Significant Findings

None to date.

Air Sampling Instruments Symposium

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Start & End Dates: *01/01/91 - 12/31/91*
Funding Level: *\$3,000 (\$3,000 Cum)*

Importance to Occupational Safety and Health

The ACGIH, with the technical input of its Air Sampling Instruments Committee, sponsored a symposium entitled: ACGIH Symposium on Air Sampling Instruments: Applications, Technology, Criteria, and Standards.

This was an ideal forum for bringing worldwide interests together, all at one time and in one place. Distinctions and separations between air measurements for purposes of industrial hygiene, air pollution, indoor air, health physics, hazardous waste, etc. are rapidly disappearing, and the unity of the science and practice in this field needs emphasis and accommodation. The importance of this subject it resides in the fact that control of the environment begins and ends with measurements: first, recognition that an unreasonable health risk is present, and last, assurance that the hazard has been abated. In between, measurements guide the application of engineering controls.

To accomplish all of these objectives, a symposium was convened during October–November 1991 with those who regulate and set standards, together with users, designers, manufacturers, and vendors of instruments that are used for air sampling and analysis. The symposium encompassed three major activities:

1. Presentations of invited and submitted technical papers on regulatory initiatives, setting of standards, and measuring instruments (operating principles, capabilities, feasible future improvements and applications, standards, and performance criteria).
2. Exhibits of commercial and laboratory-constructed instruments.

3. Formal technical workshops and clinics, scheduled and conducted by individual instrument manufacturers, to instruct and advise past and future purchasers how to use and get the most out of their equipment.

Personal Benzene Vapor Detection Device

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Program Area: *Other Occupational Needs*
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Start & End Dates: *09/30/91 - 03/31/92*
Funding Level: *\$47,182 (\$47,182 Cum)*

Importance to Occupational Safety and Health

Benzene is a volatile liquid that is soluble in lipids. It can be absorbed into the body following ingestion, inhalation, and actual contact. Available data from both animal and human studies indicate that after absorption benzene must undergo metabolic transformation to exert its toxic effects. Metabolism of benzene occurs primarily in the liver, however, the enzymes necessary for metabolism are also present in the bone marrow. The lymph system is also a target for benzene toxicity.

In humans, the toxicity of benzene is characterized by a decrease in the various circulating blood cells. Some persons have developed myelogenous leukemia. Benzene can also cause neurotoxic effects; it is also genotoxic, causing structural changes to the chromosomes. The carcinogenicity of benzene has been demonstrated in rats and mice. Epidemiological studies suggest that long-term, low-level exposure to benzene is carcinogenic in humans. The EPA has classified benzene as a human carcinogen.

Humans can be exposed to benzene in the environment, in consumer products, and in the workplace. The greatest exposures levels are found in the workplace. Most people are exposed to benzene vapor in tobacco smoke and in automobile gasoline. Consumer products containing benzene include glues, adhesives, household cleaning products, paint strippers, art supplies, tobacco, and gasoline. Exposure at the gas pump could be significant as can exposure in the rubber industry, oil refineries,

chemical plants, the shoe industry, and gasoline storage facilities.

In order to assess this increased risk in a more quantitative manner, it is desirable to have available a personal monitoring device that will allow a person to determine the level of his/her exposure to benzene in various locations, such as the workplace, home gasoline stations, etc. This device would integrate the exposure to benzene over a period of hours, days, weeks, or months giving the person direct quantitative information concerning their exposure to benzene. This device, at the end of the designated time period, would be removed, placed in an FTIR spectrometer, and the level of exposure to benzene determined by rapid analysis.

Objectives

- Development of a porous nylon coating that is specific to the adsorption of benzene.
- Development of a thin (a few microns thick) and uniform nylon coating on the optical fiber.
- Determination of the saturation capacity of the nylon coating for benzene.
- Detection of low concentrations of benzene vapor with the coated optical fiber by attenuated total reflection spectroscopy.

Methodology

This report describes the Phase I work performed to develop a personal wear badge for the accumulated exposure detection of benzene vapor. The badge would consist of small sections of optical fiber that have been coated with a membrane specific for the adsorption of benzene vapor. After exposure, the badge is placed in a Fourier Transform Infrared (FTIR) spectrometer, and the infrared spectra of the surface derivative of benzene is determined. The quantitative exposure levels would be determined by the peak intensities after first having been standardized. The sensor can be used again and cumulative exposure determined as a function of time. These new devices would allow rapid determination of exposure levels.

Benzene vapor has primary adsorption bands in the mid-IR region. However, the concentration of benzene in the workplace is too low to be measured accurately with FTIR spectroscopy. The fiber surface modifications are based on the incorporation of benzene reactive compounds contained in a very thin, surface area porous membrane coating applied to the fiber surface. The coating will enhance the concentration of benzene at the surface of the fiber. The surface coating technology will be developed and demonstrated on an active fiber system in the Phase I program. The badge will be engineered in such a

way as to allow simple removal of the fiber module for direct insertion into the FTIR spectrometer.

Significant Findings

Small sections of optical fiber were coated with a membrane specific for the adsorption of benzene vapor. After exposure the fiber was placed in a Fourier Transform Infrared (FTIR) spectrometer and the infrared spectra of the surface bound benzene was obtained. The qualitative exposure levels were determined by peak intensities. Benzene was detected at a concentration of 100,000 ppm. Dichlorobenzene was also detectable (80,000 ppm) and could be differentiated from benzene by unique absorbance peaks. The sensor was reusable and the cumulative exposure was determined as a function of time. The sensor modifications were based on the incorporation of benzene absorbing compounds contained in a thin, high surface area porous membrane coating applied to the fiber surface. The surface coating technology was developed and demonstrated on an active fiber system. A sensor cell was designed to allow handling and direct insertion into the FTIR spectrometer.

The sensor portion of a chalcogenide fiber was coated with silicalite S-115 (Zeolite) to concentrate the benzene vapor into the region, within 5 μ of the surface, where the evanescent wave propagates outside the optical fiber. Benzene could be detected at levels of 100,000 ppm and the coating retained the benzene for a period of days. Membranes of polyethylene and nylon filled with zeolite were successfully applied to a silver halide fiber and benzene at 100,000 ppm concentration could be detected.

Development of a Real Time, Continuous Isocyanates Monitor

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Program Area: *Other Occupational Needs*
Grant Number: *1 R43 OH02913-01*
Start & End Dates: *09/30/91 - 06/30/92*
Funding Level: *\$48,868 (\$48,868 Cum)*

Importance to Occupational Safety and Health

Isocyanates exposure and sensitization to isocyanates has been implicated as a major cause of occupational respiratory disorders. The use of isocyanates in a broad spectrum of uses including urethane foam production and isocyanates (polyurethane) coatings application exposes a significant population to the effects of these materials. NIOSH estimates a population at risk in the workplace of 50,000 to 100,000 persons with potential for adverse respiratory response to these materials.

At present, there is no available continuous, real time monitor for isocyanates in workplace air with adequate sensitivity and specificity to measure various isocyanates at target levels of 0.02 ppm.

The monitor being developed by ADA Technologies, Inc. will measure the isocyanates in air (in both vapor and aerosol form) and will have the potential to provide compound-specific analyses to differentiate the commonly used isocyanate species.

Objectives

The objective of the Phase I effort is to demonstrate the technical feasibility of using a unique spectral emission technique to detect and quantify various isocyanates in air with a detection limit of 0.02 ppm. The research effort will demonstrate the sensitivity of the technique for aerosol and vapor forms of toluene diisocyanate (TDI), hexamethylene diisocyanate (HDI), and similar compounds used in industry and acting as significant isocyanate exposure risks. The testwork will also address the effect of common interferents on the detection and quantitation of isocyanates and will investigate the opportunity of the method to differentiate among various isocyanate species.

The results of the successful Phase I work will be to produce a detailed system design for further demonstration in Phase II and, ultimately, for commercialization as a widely applicable real-time monitor for isocyanates in various industrial settings in Phase III.

Methodology

The Phase I effort will expand on preliminary exploratory testwork at ADA Technologies which had demonstrated the feasibility of detecting isocyanates in air at low-ppm (but not sub-ppm) levels by employing a unique reaction of isocyanate species with oxidants to produce light.

The laboratory tasks will begin with fabrication of a sampling and reaction system to acquire known concentrations of isocyanates in air and to expose these samples to conditions which result in the

production of light at intensities and spectral ranges related to the concentration and chemical composition of the active species.

The system will then be used in a series of parametric tests to define the best operating conditions under which low levels of isocyanates (0.02 ppm) can be reliably detected and quantified. The tests will also include protocols which address the response of the system to common interferents (nitrogen oxides, organic amines, and similar nitrogen-containing species) and methods to minimize or eliminate interferences if they are actually found to impact isocyanates detection and measurement.

The optimized system will be tested to determine its potential for discriminating among the commonly used isocyanate species and to confirm the individual detection limits for these materials.

Finally, the results of the Phase I effort will be detailed in a Final Report which will include a design for a prototype isocyanates monitor to be fabricated, tested, and demonstrated in Phase II.

Significant Findings

The Phase I laboratory program demonstrated the technical feasibility of an innovative chemiluminescent technique for the selective detection of isocyanate species in air at levels as low as 0.02 parts per million (ppm). Results of the Phase I work were reported in the Final Report of this project on schedule.

The Phase I testwork demonstrated the following aspects of the proposed isocyanates monitoring concept:

- Toluene diisocyanate in room air could be detected at a level of 0.02 ppm by the chemiluminescent technique.
- Aliphatic isocyanates were detected but with detection limits higher than the target 0.02 ppm.
- The monitor provides nonspecific analysis of isocyanate species and thus serves as a total isocyanates monitor.
- The preferred source of reactive oxygen for the monitor is high purity oxygen, rather than the originally proposed room air.
- Chemical interferent effects are minimal for typical organic compounds (aromatic hydrocarbons, alcohols, ketones, etc.) and inorganic species such as atmospheric moisture, carbon dioxide, nitrogen oxides, and ammonia. Organic amines present interferent response in the monitor, but with appreciably lower sensitivity than the isocyanates.

The technical feasibility of the proposed chemiluminescent isocyanates detection and analysis technique was thus demonstrated, interferent effects were shown to be minimal, and adequate data was collected in the Phase I effort to permit the development of a Phase II work plan to further demonstrate the commercial potential of this innovative isocyanates monitoring technique.

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 – 03/29/93*
Funding Level: *\$49,680 (\$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 will complement monitoring studies and will 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 may 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 first stage of research is to develop an approach that can be used to predict the dispersion of chemicals in two specific indoor settings. The goal of subsequent research would be to extend the model to generic settings that can be interactively prescribed by individuals interested in assessing indoor air quality.

Methodology

The two investigations of indoor air monitoring that are to be modeled include a study of toluene diisocyanate in a polyurethane manufacturing facility and nitrogen dioxide produced in steel cutting operations. The studies will be carefully reviewed and follow up investigation will be used to discern information pertinent to pollutant dispersal. These case studies require an innovative modeling approach to account for the heterogeneous conditions that are typical of large indoor workplaces in which pollutants may be introduced or removed at numerous locations. Control volumes will represent subregions of the workplace that can reasonably be assumed to be well-mixed, and linkages between control volumes will specify the transport and dispersion of pollutants throughout the workplace. Each case study will require a characterization of source emissions. Air flow patterns will be used to estimate the movement of chemicals within the workplace. Chemical reactions, ventilation, and deposition to surfaces will be treated as removal mechanisms. Model equations will be developed that include the processes relevant to introduction, dispersion, and elimination of the chemicals of interest in the workplace. Interactive system dynamics software will be used to simulate concentrations of toluene diisocyanate and nitrogen dioxide, and these modeled results will be compared with the measurements obtained in the indoor air studies.

Significant Findings

None to date.

Development of a Low-Cost Ethylene Oxide Detector

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Program Area: *Other Occupational Needs*
Grant Number: *2 R44 OH02662-02A1*
Start & End Dates: *09/30/88 – 05/31/92*
Funding Level: *\$396,315 (\$443,222 Cum)*

Importance to Occupational Safety and Health

Regulations governing the exposure of employees to ethylene oxide (EtO) have become stricter in

recent years due to studies which have established the mutagenicity and animal carcinogenicity of EtO. There is a need for a new EtO monitor because commercially available instruments and devices for measuring EtO do not address the needs of EtO users or the Occupational Safety and Health Administration (OSHA) requirements for monitoring work areas where EtO is used. The EtO monitor being developed by ADA Technologies, Inc. (ADA) will combine the low-cost and low-maintenance characteristics of a solid state detector-based monitor with the specificity and sensitivity of a gas chromatograph. The monitor will alert employees of EtO levels exceeding the Permissible Exposure Level, the excursion limit, and the action level.

Objectives

The goal of this research and development program is to design, build, and test a prototype EtO monitor that is versatile enough to be used as an inexpensive hand-carried portable monitor or a wall-mounted area monitor. The prototype EtO monitor will operate continuously as a direct-reading instrument, employing a rugged solid state semiconductor sensor. A gas chromatography column will provide the specificity for EtO that is lacking in existing low-cost commercial real-time monitors. The prototype will be capable of providing an updated digital concentration readout once every minute and displaying an audible/visual alarm when the EtO concentration exceeds one of two preset levels. The final instrument design will incorporate low-cost components so that the anticipated price of a commercial version will not exceed \$4,000.

Methodology

The Phase II program developed, optimized, and tested the innovative ETO monitor and culminated in a Final Phase II Report as the deliverable item from this project.

The operation of the GC component of the monitor with room air as carrier gas and a catalytic combustor with a membrane dryer as gas conditioning modules was demonstrated.

A microprocessor system custom configured for operating the valving in the monitor and for logging sample analyses was successfully demonstrated in continuous operation of the prototype monitor for periods ranging from days to weeks.

Peak detection algorithms were developed for the microprocessor and shown to be functional in detecting and quantitating ETO elution peaks with a detection limit of about 0.2 ppm.

The alarm functions for the monitor (at 0.5 ppm and 5.0 ppm ETO in air) were confirmed and the

microprocessor log was structured to also log alarm level and time of alarm.

The laboratory tests identified the optimum operating conditions for the chromatographic separation of ETO from common interferents including isopropyl alcohol and chlorofluorocarbons frequently used as ETO diluent in sterilizer mixes.

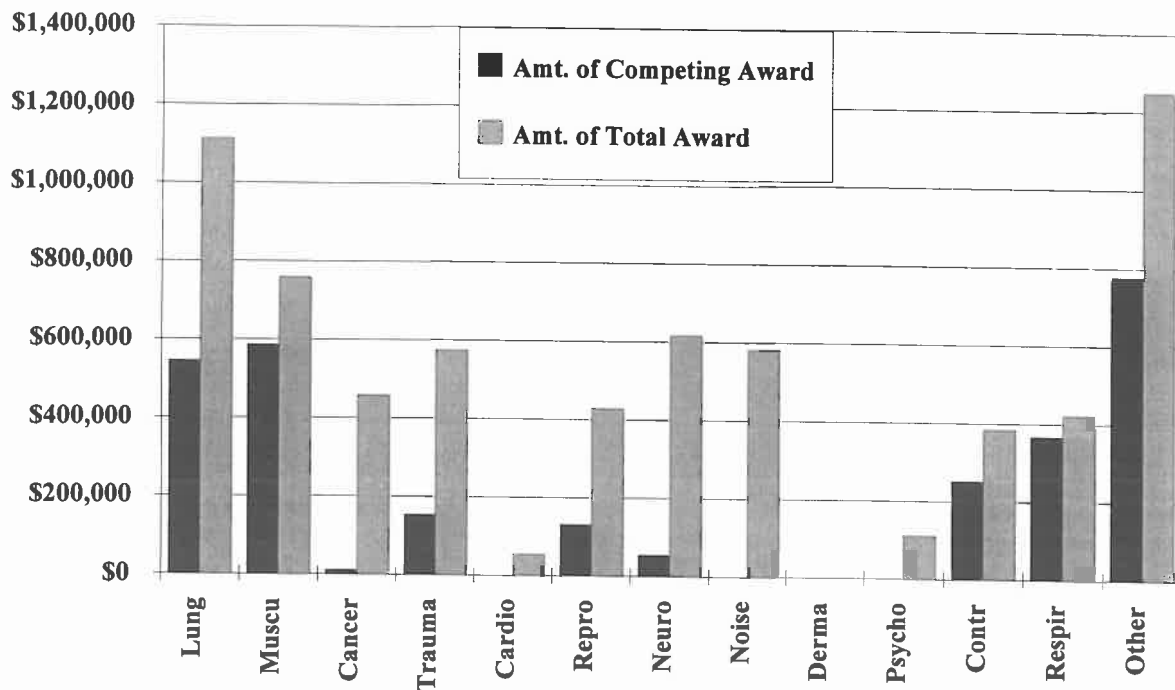
A final instrument design package and test description was prepared for soliciting Phase III commercialization interest in this monitor.

Significant Findings

The Final Phase II Report of this project notes the following significant findings:

- The chromatographic separation of ETO in room air from common organic contaminants was demonstrated.
- The use of a semiconductor sensor (tin oxide type) in the monitor was demonstrated to be a selective sensor for ETO relative to other atmospheric gases.
- The operation of the monitor under custom configured microprocessor control was shown to be an efficient way to both operate the switching valves in the monitor and to log performance data for the system on a daily or weekly basis.
- Downloading of data from the Phase II monitor to a PC was successfully demonstrated.
- A detection limit of about 0.2 ppm ETO in room air was demonstrated for the Phase II monitor in unattended operation on a weekly basis.
- Based on the results of the Phase II testwork and system design details, the projected sales price of a commercial model of the monitor is about \$5,000.

FY92 Grant Awards by Program Area Competing and Total Dollars



Program Area	Competing Awards		Total Awards	
	Number	Amount	Number	Amount
Lung	4	\$544,146	9	\$1,112,543
Musculoskeletal	4	\$585,882	7	\$759,332
Cancer	1	\$11,458	7	\$457,522
Trauma	2	\$152,957	4	\$574,832
Cardiovascular	0	\$0	1	\$54,000
Reproductive	3	\$130,888	4	\$428,066
Neurotoxic	1	\$53,987	4	\$617,949
Noise	0	\$0	3	\$581,843
Dermatological	0	\$0	0	\$0
Psychological	0	\$0	1	\$110,567
Control Techniques	4	\$251,238	6	\$383,890
Respirator	3	\$367,209	4	\$420,960
Other	8	\$778,564	14	\$1,251,261
TOTAL	30	\$2,876,329	64	\$6,752,765

<u>Grantee Institution</u>	<u>Principal Investigator</u>	<u>Page</u>
Cincinnati, University of	Richard J. Wickstrom	77
Columbia University	David J. Brenner, Ph.D.	37
Iowa State University	Michael E. Drues	157
Johns Hopkins University	Robert Frank, M.D.	110
Minnesota, University of	Lisa M. Brosseau, Sc.D.	131
New York University	Judy Q. Xiong, Ph.D.	159
North Carolina, University of	Irva Hertz-Picciotto, Ph.D.	158
Ohio University	Marjorie E. Nelson, M.D.	79
Utah, University of	Daniel R. Baker	48
Washington, University of	Harvey Checkoway, Ph.D.	88

Conference Grants (R13)

New York University	Beverly S. Cohen, Ph.D.	160
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Small Business Grants (R43, R44)

ADA Technologies, Inc.	David E. Hyatt, Ph.D.	160
ADA Technologies, Inc.	David E. Hyatt, Ph.D.	163
Cambridge Environmental, Inc.	Stephen G. Zemba, Ph.D.	163
Dynaflow, Inc.	Clinton E. Brown	131
EXOS, Inc.	Beth Ann Marcus, Ph.D.	49
Foster-Miller, Inc.	Mark A. Druy, Ph.D.	161
Full Circle Systems	Samuel V. Johnson, Ph.D.	118
Rehabilitation Technology Inc.	Christopher C. Johnson	120
Vermont Sensing	Peter J. Kajenski, Ph.D.	119



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