CDC

CENTERS FOR DISEASE CONTROL

NIOSH

Research and Demonstration Grants

Annual Report Fiscal Year 1991

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

NIOSH

RESEARCH AND DEMONSTRATION GRANTS

FISCAL YEAR 1991

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

May 1992

DISCLAIMER

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

DHHS(NIOSH) Publication No. 92-109

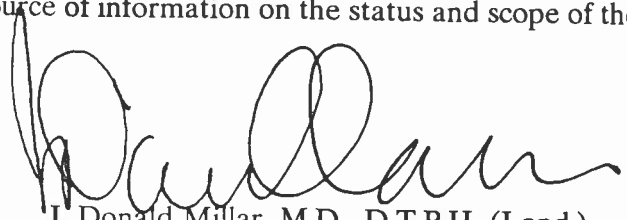
FOREWORD

The National Institute for Occupational Safety and Health (NIOSH) is required 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. In addition to a substantial program of intramural research, NIOSH supports outstanding extramural research as a major component of its scientific activity.

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 as the first ten entries in Section H. ("Funding Priorities") in the program announcement included in this report (pages 4-10). In addition to the leading occupational diseases and injuries, our high priorities also include research on engineering control methods and respiratory protection because of the crucial importance of these 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 scientific and professional disciplines. Our extramural research program is an important means of encouraging progress in these preventive efforts.

Because the strengths of the extramural research program are the creativity and special skills available in the scientific community, we publish this report to stimulate submission of proposals for research of high quality on significant problems of occupational safety and health. We invite the interest of investigators in the biomedical sciences, engineering, and related disciplines. By including descriptions of all active grants during fiscal year 1991 (October 1, 1990 to September 30, 1991), we intend to provide a readily available source of information on the status and scope of the research grants program of NIOSH.



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

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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 9,400 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?

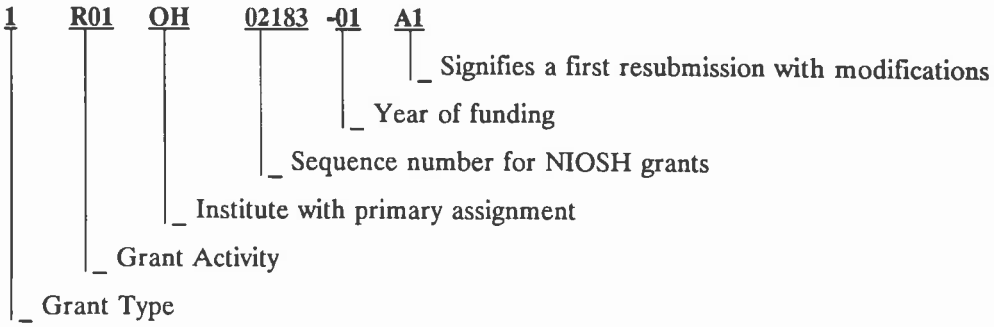
Contact NIOSH at the following address and telephone number:

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
National Institute for Occupational Safety and Health

ANNOUNCEMENT NUMBER 923

RESEARCH AND DEMONSTRATION GRANTS
RELATING TO OCCUPATIONAL SAFETY AND HEALTH

A. INTRODUCTION

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

B. AUTHORITY

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

C. ELIGIBLE APPLICANTS

Eligible applicants include non-profit and for-profit organizations. Thus, universities, colleges, research institutions, and other public and private organizations, including State and local governments and small, minority and/or woman-owned businesses, are eligible for these research and demonstration grants.

D. AVAILABILITY OF FUNDS

The support mechanisms for this program are the individual research project grants (R01); demonstration project grants (R18); special emphasis research career award (SERCA) grants (K01); and small grants (R03). Approximately $6,747,847 is available for FY 1992 to fund these grants: $4,078,575 for non-competing continuation awards and $2,669,272 for new and competing renewal awards. The estimated breakdown for the new and competing renewal awards is as follows: R01 and R18 grants - 13 awards for $2,160,772 (total costs of these awards range from $50,000 to $250,000 with the average award being about $130,000); K01 grants - 4 awards for $216,000; and R03 grants - 13 awards for $292,500.

E. BACKGROUND

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

Additional guidance is found in the document, "Healthy People 2000: National Health Promotion and Disease Prevention Objectives." The document contains measurable objectives and strategies for creating a healthier society over the next decade. The objectives and strategies are organized broadly into 3 major categories: Health Promotion, Health Protection, and Preventive Services. There are a total of 22 priority areas. The tenth priority area, "Occupational Safety and Health," is applicable to this program announcement. Overall objectives in this priority area are to reduce work-related deaths, injuries, and illnesses. Research is needed on the following: identification of new stressors affecting workers, new measurement tools for assessing worker exposures, biomarkers of workers' exposure and response, identification of populations and individuals at special risk of work-related disease and injury, mechanisms of insult and intoxication, hazard surveillance, disease and injury identification and surveillance, development of control approaches, and effective use of controls.

F. PURPOSE

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

G. MECHANISMS OF SUPPORT

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

1. Research Project Grants (R01)

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

2. Demonstration Project Grants (R18)

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

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

   The SERCA grant is intended to provide opportunities for individuals to acquire experience and skills essential to the study of work-related hazards, and in so doing create a pool of highly qualified investigators who can make future contributions to research in the area of occupational safety and health. SERCA grants are not intended either for individuals without research experience or for productive, independent investigators with a significant number of publications and of senior academic rank. Moreover, the award is not intended to substitute one source of salary support for another for an individual who is already conducting full-time research; nor is it intended to be a mechanism for providing institutional support.

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

This non-renewable award provides support for a three-year period for individuals engaged in full-time research and related activities. Awards will not exceed $50,000 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) and a letter from the supporting institution agreeing to the minimum 60 percent time commitment to the research project for three years.

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), and 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).

Applicants to this program should type "NIOSH Small Grant Program" in item 2 on the face page of the PHS-398 application form or at the top of the face page of the PHS-5161 form.

H. FUNDING PRIORITIES

The NIOSH program priorities, listed below, are applicable to all of the above types of grants listed under "G. MECHANISMS OF SUPPORT." These priority areas represent the leading diseases and injuries related to risks on the job, and NIOSH intends to support projects that facilitate progress in preventing such adverse effects among workers. The conditions or examples listed under each category are selected examples, not comprehensive definitions of the category. Investigators may also apply in other areas related to occupational safety and health, but the rationale for the significance of the research to the field of occupational safety and health must be developed. Potential applicants with questions concerning the acceptability of their proposed work are strongly encouraged to contact the individuals listed in this announcement under "O. WHERE TO OBTAIN ADDITIONAL INFORMATION." The NIOSH Program Priorities are:

- 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 infraction
- 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; mal-adaptive behavior and lifestyle patterns; aggression; stress and post traumatic stress disorders; substance abuse
- Control Techniques: new technology performance evaluation, preconstruction review, equipment redesign, containment of hazards at the source, fundamental dust generation mechanisms, machine guarding/avoidance methods, explosion control, removal of emissions after generation, dispersion models, monitoring and warning techniques, technology transfer
- Respirator research: new and innovative respiratory protective devices, techniques to predict performance, effectiveness of respirator programs, physiologic and ergonomic factors, medical surveillance strategies, psychological and motivational aspects, effectiveness of sorbents and filters, including chemical and physical properties

I. INCLUSION OF MINORITIES AND WOMEN IN STUDY POPULATIONS

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

J. APPLICATIONS SUBMISSION DEADLINES AND REVIEW DATES

Applications should be submitted on Form PHS-398 (revised 9/91). State and local government applicants may use Form PHS-5161-1 (revised 3/89); however, Form PHS-398 is preferred. Forms should be available from the contacts listed under "O. WHERE TO OBTAIN ADDITIONAL INFORMATION," or from:

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

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

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

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

Research and Demonstration Project Grants:

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

*Competing continuation deadlines are 1 month later.

SERCA and Small Grants

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

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

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

K. EVALUATION CRITERIA

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

1. The initial (peer) review is based on scientific merit and significance of the project, competence of the proposed staff in relation to the type of research involved, feasibility of the project, likelihood of its producing meaningful results, appropriateness of the proposed project period,adequacy of the applicant's resources available for the project, and appropriateness of the budget request.

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

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

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

   - The review process will consider the applicant's scientific achievements, the applicant's research career plan in occupational safety and health, and the degree to which the applicant's institution offers a superior research environment (supportive nature, including letter(s) of reference from advisor(s) which should accompany the application).

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

   - The review process will take into consideration the fact that the applicants do not have extensive experience with the grant process.

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

   - The results of the initial review.
   - The significance of the proposed study to the 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 "O. WHERE TO OBTAIN ADDITIONAL INFORMATION."

L. TECHNICAL REPORTING REQUIREMENTS

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

M. EXECUTIVE ORDER 12372 REVIEW

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

N. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER (CFDA)

The Catalog of Federal Domestic Assistance number is 93.262.

O. WHERE TO OBTAIN ADDITIONAL INFORMATION

For Technical Information Contact:

Roy M. Fleming, Sc.D.
Associate Director for Grants
National Institute for Occupational Safety and Health
Centers for Disease Control
1600 Clifton Road, N.E.
Building 1, Room 3053, Mail Stop D-30
Atlanta, Georgia 30333
Telephone: (404) 639-3343

For Business Information Contact:

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

Epithelial Surface Proteins: Markers of Cancer Risk

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

Program Area: *Occupational Lung Diseases*
Grant Number: *5 R01 OH02114-03*
Start & End Dates: *01/01/86 - 12/31/90*
Funding Level: *$114,499 ($408,279 Cum)*

Importance to Occupational Safety and Health

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

Objectives

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

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

Finally, dietary history and serum samples were assessed to quantify ingestion of carotenoids, substances which may have antiinflammatory and cancer-preventive properties.

Methodology

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

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

Finally, we related dietary ingestion of carotenoids to both the presence of metaplasia and to inflammation in BAL fluid. These analyses are in progress at present.

Significant Findings

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

Metaplasia: Metaplasia was detectable in bronchial biopsies obtained from half of the study population. We attempted to relate smoking history and asbestos exposure history to the presence of

metaplasia by separating the population into those with and without metaplasia and applying appropriate statistical tests. Smoking history was associated with metaplasia because worse grades of metaplasia were seen in active smokers. Asbestos exposure history was not associated. We quantified free secretory component and keratins by micro ELISA. Free secretory component values for the population were similar to those of normal controls. Keratins were absent from normal controls and detectible in 54% asbestos workers. However, there is no relation between keratins in bronchoalveolar lavage fluid and the presence of metaplasia detectible by bronchial biopsy. Finally, biopsy evidence of severe metaplasia was associated with the presence of acute inflammatory cells in lavage fluid. This persisted after stratification of the population by smoking status. Among the variables analyzed, only acute inflammatory cells were significantly related to metaplasia by logistic regression.

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

Publications

Merrill WW, Carter DY, Cullen MR: The Relationship Between Bronchial Imflammatory Cells and Large Airway Metaplasia. Chest 100:131-135, 1991

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Influence of Particles on Occupational Lung Disease

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

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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

Male Syrian Golden hamsters are known to be susceptible to the formation of lung tumors by BaP-coated particles. Alveolar macrophages (AM) were isolated by tracheal lavage from male Syrian hamsters (100-150 g, 8-9 wks old). The hamsters were anesthetized with sodium pentobarbital i.p. (0.5 ml 1% solution), and exsanguinated by cutting the abdominal aorta. The trachea was cannulated with a blunt 18 gauge needle and attached to a 3-way stopcock. The lungs were lavaged 8 times *in situ* with calcium and magnesium-free phosphate buffered saline (PBS pH = 7.2) at a volume equal to 4-5 ml. AMs were separated from the lavage fluid by centrifugation at the rate 200x g for 10 min. at room temperature. After centrifugation, supernatants were discarded and the pellets were resuspended with RPMI-1640 medium containing 0.1% gentamicin, 25 mM L-glutamine, 0.2% sodium bicarbonate and 2 mg/ml bovine serum albumin (pH = 7.2) (BSA). An aliquot of the cell suspension was removed to determine viability and the numbers of cells by trypan blue staining procedure. Another aliquot of the cell suspension was used to identify the purity of AM by using cellular differential staining (Diff-Quik stain set Sci. Product Inc.). About $1x10^6$ cells with 2.5 ml RPMI-1640 were plated for each petri dish. After 1.5 hr, the unattached cells were removed. The cells 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 and protein to the release of metabolites from the cell. Metabolite mixtures with and without BaP will then be analyzed by bacterial mutagenesis assays with and without S9.

Significant Findings

The comparative viability of the AM in the presence of ferric oxide, aluminum oxide and four forms of silica [(crystalline, and three forms of amphorous silica (precipitated, fumed, and gelled)] was undertaken to determine noncytotoxic doses during phagocytosis. Doses of particles ranged from 0.0 to 0.5 mg. The viability of the AM in the presence of ferric oxide and aluminum oxide up to the highest dose was similar to controls. After 24 and 48 hrs, the viability of the AM was approximately 80 and 70% respectively. In the presence of silica the viability of the AM was similar to controls up to 0.01 mg and approximately 80 and 70% at 24 and 48 hrs respectively. At doses of 0.05 mg and 0.1 mg of crystalline, precipitated or fumed silica, at 24 hours the viability of the AM dropped to 70 and 45%, respectively, and at 0.5 mg the viability was 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. At the present time, studies are underway using particles in the presence of cytochrome C to monitor changes in the basal metabolic activity of the AM by the reduction of cytochrome C with time as a measure of phagocytosis. For 0.1 mg Fe_2O_3 dose, the metabolic activity ranged from 0.67 nmols of reduced cytochrome C/10^6 cells at 24 hours to 4.7 nmols/10^6 cells at 48 hours whereas at 0.5 mg Fe_2O_3 the metabolic activity of the AM ranged from 8.5 nmoles/10^6 cells at 24 hrs to 25.9 nmols/10^6 cells at 48 hrs. For crystalline silica at 48 hrs the metabolic activity of the AM was 21 nmoles/10^6 cells for a 0.1 mg dose and 8.4 nmoles/10^6 cells for a 0.05 mg dose. Similar studies are being initiated with rat AM.

Metabolism studies of BaP and BaP coated particles are in progress with the major metabolites being the dihydrodiols of BaP. ^{32}P-postlabeling studies are underway to investigate the effects of particles on BaP adduct patterns of DNA in the alveolar macrophage.

Ferric oxide was of respirable size with a particle size distribution of greater than 90% less than 5 microns and, over 70% less than 2.5 microns with a mass median diameter of 1.37 microns. Crystalline silica was of respirable size with a particle size distribution of greater than 99% less than 5 microns, and over 90% less than 2.5 microns. The crystalline silica has a median diameter of 0.83 microns and a surface area of 2.99 m^2/g. Silica gel is 60% by weight less than 4.7 microns in diameter; 99% of the particles are less than 5 microns and have a geometric mean diameter of 0.27 microns. The precipated silica is 46% by weight less than 4.7 microns in diameter; 98% of the particles are less than 5 microns and have a geometric mean diameter of 0.38 microns. The fumed silica is being analyzed. The aluminum oxide is 99% less than 5.0 microns with a median diameter of 0.36 microns. It should be noted that no crystalline silica was found to be present in the amphorous forms of silica.

Pilot Project to Assess Mortality Among Former Chromium Smelter Workers

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

Program Area: *Occupational Lung Diseases*
Grant Number: *5 R01 OH02298-02*
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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.

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 5,056 workers were identified. 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

Despite the lack of current addresses, we have been able to determine the vital status and locate at least 60% of the cohort. Because of the nature of records we had available, we do not yet know what percentage of the remaining 40% of the cohort not located has been notified but has not responded, or if alive has not been notified, or has died.

We have reached a 60% follow-up before we have had the opportunity to use two large national data bases, the Social Security Administration benefit file, and the National Death Index. After using these data bases, we expect our percentage of follow-up to be comparable to other mortality/high risk worker notification projects.

Our impression from contact with individuals in the cohort and a more formal evaluation is that notification was well accepted and in fact, appreciated by a large percentage of the cohort. At this time, 946 (29%) of the cohort that may still be alive have responded to our questionnaires. Fifty-three percent of the respondents have indicated they wish to participate in a future medical screening program, 26% are current smokers, and 17% have perforated nasal septums.

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

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

Program Area: *Occupational Lung Diseases*
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Importance to Occupational Safety and Health

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

Objectives

1. Determine alterations in normal particle clearance for supramicron (3.0 μm diameter)

and submicron (0.5 μm diameter) particles under increasing lung burdens.
2. Quantitate the number of particles ingested by macrophages in the tracheobronchial tree and in alveoli under increading lung particle burden.
3. Determine the lung particle burden at which macrophages begin to exhibit altered properties with regard to activation, phagocytic activity, release of cytokines, and oxygen metabolism.
4. Examine paracrine mechanisms with respect to low and high particle lung burden.
5. Examine the lung for evidence of chronic inflammation and fibrosis after alteration in clearance and cell function from high lung particle burdens.

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 particle. These particles will contain either a radioactive tag (^{57}Co) or a fluorescent tag. We will follow clearance non-invasively via gamma camera imagery and serial computer stored images. We will perform serial upper airway lavage and bronchoalveolar lavage. These cells will be examined for radioactivity by well counter and for particle content by fluorescent microscopy. The collected cells will be cultured and examined for surface receptors by fluorescently tagged antibodies. Changes in functional characteristics will be investigated such as increased O_2 consumption, proinflammatory and cytotoxic activity, procoagulant activity, phagocytizing capacity and 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. Normal tracheobronchial clearance is complete in 45 hours and alveolar clearance has a half-life of 30 days for the 3.0 μm particle as determined by gamma camera imagery.
2. On instillation, 35% of the tracheobronchial macrophages contain both 0.5 μm particles and 3.0 μm particles at 1 hour post-deposition. The ratio of 0.5 μm particles to 3.0 μm particles engulfed by macrophages was the same as the number of particles deposited (400:1). No particles were found in tracheobronchial macrophages 48 hours post-deposition, indicating upper airway macrophages had cleared within 48 hours, confirming the non-invasive imagery of finding 1.
3. On instillation, 40% of the alveolar macrophages contained particles at 24 and 48 hours post-deposition with 12% containing >5 particles. By day 10, only 10% of the macrophages contained particles and only 1% had >5 particles. On inhalation, 10% of the alveolar macrophages contained particles at 24 and 48 hours post-inhalation with no macrophages containing >5 particles. By day 10, greater than 30% of the macrophages contained particles with 11% having >5 particles. By day 30, only 3% of the macrophages contained particles with no macrophages containing >5 particles. These findings suggest either macrophages are activated upon engulfing particles which subsequently render them more efficient in ingesting other particles or a subpopulation of cells exist *in situ* which react with non-immunogenic particulates.
4. Human monocyte derived macrophages (HMDMs) exhibited heterogeneity to submicron particle challenge *in vitro* and heterogeneous subpopulations have been successfully sorted. A preexisting heterogeneity to particle challenge is intrinsic to these HMDMs which sustained itself through 2 separate particle challenges. Sheep alveolar macrophages (AMs) exhibit heterogeneity to particle challenge *in vivo* and the subpopulations have been successfully sorted.
5. Particle phagocytosis results in a change in surface Fcγ receptors, a parameter associated with cell activation. After particle phagocytosis *in vitro* the HMDMs appear to down regulate FcγR III but after particle phagocytosis *in vivo*, the sheep AMs increase immune complex FcγR.
6. 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.
7. 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.
8. AMs containing greater than 5 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 particles was considerably less than the % of AMs on each of the serial bronchoalveolar lavages (BALs). This indicate 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.

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Lung Disease in Chinese Textile Workers

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

Program Area: *Occupational Lung Diseases*
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Importance to Occupational Safety and Health

This study is a longitudinal follow-up of cotton textile workers in Shanghai, China. The relevance of the knowledge gained from this work includes: the relative contributions of cotton dust and gram negative bacterial endotoxins in producing acute and chronic respiratory disease; the rate of annual decline in lung function after exposure to cotton dust; and the importance of acute, cross-shift change

in FEV_1 in predicting longitudinal loss of lung function. Determination of exposure-response for gram negative bacterial endotoxins is important not only for textile workers, but also for thousands of workers exposed to other organic dusts and environments rich in endotoxin.

Objectives

Briefly stated, the project objectives have been:

1. To determine the 10-year incidence and remission of byssinosis and non-specific respiratory symptoms among cotton textile workers, using silk workers for comparison, and to relate these findings to exposure to cotton dust and endotoxin.
2. To determine the rate of annual decline in pulmonary function in cotton workers and silk referents and relate these outcomes to various estimates of current and historical work exposures.
3. To explore the relative contributions of cotton dust and airborne gram negative endotoxin exposure in the development and progression of respiratory symptoms and pulmonary function change.
4. To explore the assumption of a cross-shift change in FEV_1 at baseline screening and subsequent development of respiratory symptoms and loss of FEV_1.

Methodology

The study is a 10-year follow-up with surveys done at years 0, 5 and 10. 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 10. The cause of death, as well as other reasons for loss from cohort, will be ascertained on all subjects.

Significant Findings

None to date.

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Airway Hyperreponsiveness Due to Cotton Bract Exposure

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

Program Area: *Occupational Lung Diseases*
Grant Number: *5 R01 OH02593-02*
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Importance to Occupational Safety and Health

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

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

Objectives

Our specific aims are:

1. To investigate if cotton bract exposure induces airway hyperresponsiveness in healthy smokers

and non-smokers. The working hypothesis is that smokers have an asymptomatic, low-level of airway inflammation that makes them more susceptible to non-specific airway hyperresponsiveness following acute exposure to cotton bract (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 19 healthy non-smokers (NS) to CBE inhalation on 5 consecutive days, and on a 6th day, following a 2-day interruption of CBE inhalation. Partial and maximal expiratory flow volume loops were obtained prior to (BL) and at 15-minute intervals for 2 hrs after CBE inhalation. The average maximal MEF40(P) percent decrement from BL (AMMPDB was calculated for each of the 6 days; the AMMPDB for each day was 14.3 ± 3.4% on day 1, 9.2 ± 4.0% on day 2, 11.3 ± 3.8% on day 3, 8.7 ± 3.4% on day 4, 9.2 ± 3.5% on day and 13.5 ± 3.6% on day 6. Longitudinal data analysis, comparing the AMMPDB from day 1 with the AMMPDB from each of the subsequent days revealed that the AMMPDB was greater on day 1 than on day 2 ($p=.11$), day 4 ($p<.05$) and day 5 ($p=.07$). No significant difference in AMMPDB was noted between day 1 and day 6 ($p=.76$). No significant difference in AMMPDBs was noted between non-Monday days. Conclusion: (1) Acute decrements in expiratory 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 51 healthy smokers (HS) (mean=11.4 + 1.3 pack years) and 20 healthy nonsmokers (HNS) ages 18-40. Partial and maximal expiratory flow volume loops were obtained prior to bronchial challenge (BL); at fifteen minute intervals following CBE inhalation; and after each inhaled incremental dose of MC up to a maximal dose of 200 mg/ml.

In 4 of 20 HNS versus 27 of 51 HS ($p<.01$) a > 20% decrement in MEF20(P) occurred within 2 hours of CBE inhalation. The mean BL MC log (PD20MEF40(P)) +1 was significantly lower in Smokers vs Non-smokers, 1.75 vs 2.84 ($p<0.001$). Two hours after CBE inhalation, no significant change in bronchial responsiveness to methacholine was noted in the HNS. However, in the HS a lower log (PD20MEF40(P)) +1 for methacholine was noted after CBE challenge; 1.75 ± 0.14 vs. 1.37 ± 0.16 ($p=0.004$). 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.

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A Rational Method for Sampling Airborne Fibrogenic Dust

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

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

Methodology

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

Significant Findings

Because there are several types of membrane filters that can be used for aerosol sampling, it was decided to test the efficiency of aerosol recovery from three main types, i.e., MSA PVC, Nuclepore, and Teflon. The results indicated that the PVC filters were associated with the highest recovery efficiency followed by the Nuclepore and Teflon. After normalizing recovery efficiencies to that of PVC, the obtained values were 100% for PVC with a coefficient of variation (CV) of 2.8%, 96.5% for Nuclepore with a CV of 3.9% and finally 88.9% for Teflon with a CV of 5.4%. Therefore, MSA PVC membrane filters are utilized in all experimental procedures.

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

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

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Silicosis and Pulmonary Cancer

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

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Grant Number: *5 R01 OH02726-02*
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Importance to Occupational Safety and Health

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

Objectives

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

Methodology

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

Significant Findings

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

Coal Dust Particle Size and Respiratory Disease

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

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Grant Number: *5 R01 OH02761-02*
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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. Several mines will be visited and exposure to miners employed in the targeted occupations will be monitored using a personal cascade impactor. Using a deposition model for pulmonary aerosols, the respirable and tracheo-bronchial dust fractions will be calculated for each occupation. These fractions will then be used in conjunction with previously developed estimates of respirable dust concentrations to estimate respirable and tracheo-bronchial dust cumulative doses. Exposure response functions using the alternative dose metrics will then be compared.

An alternative method for summarizing exposure over time will be developed that accounts for non-linear effects of exposure concentration and time since exposure. This new dust metric will then be estimated using the respirable and tracheo-bronchial dust estimates developed above.

Significant Findings

Preliminary analysis of personal cascade impactor studies from three mines suggest that the variability of particle size distributions within occupations is as great or greater than variability between occupations. If this finding is corroborated in additional studies, it would 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.

Detecting Lung Overload by Magnetometry

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

Program Area: *Occupational Lung Diseases*
Grant Number: *5 R01 OH02772-02*
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Importance to Occupational Safety and Health

Rats chronically exposed to high concentrations of a variety of insoluble dusts develop lung overload in which chronic inflammation occurs in the lungs

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

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

Objectives

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

Methodology

The first year of the project was devoted to the development and testing of magnetometry and other systems needed to perform the planned research. In the future, small groups of animals will be exposed by inhalation to different amounts of a magnetic dust and an "inert" dust (TiO_2). The degree of overload will be characterized by the clearance of radioactive tracer particles, detection of chronic lung inflammation, and limited histology. Magnetometry will provide measurements of the lung burden of magnetic particles, the fraction in mobile cells, and lung clearance rates. Changes in these parameters with degree of overload by the magnetic dust or TiO_2 (with a small amount of magnetic dust to allow magnetometry) will allow determination of which functional parameters are most useful in detecting lung overload. Changes in these parameters with other experimental variables will allow determination of whether confounding factors related to species, animal age, length of time since exposure to the magnetic dust, or length of time since exposure to the nonmagnetic dust might complicate the interpretation of the results of similar measurements in humans.

Significant Findings

Several approaches to performing magnetometry on rodents were tested to determine which yielded measurements of the highest quality. The system which was developed magnetizes the dust in an animal's lungs with a short, strong pulse and starts collecting data on the remanent magnetic field surrounding the lungs within seconds. As predicted, the magnetic signal has been shown to be nearly independent of the location of the magnetic dust within the lungs, so total lung burdens of magnetic dust can be measured more directly than with systems which have been described in the literature. This magnetometry system has been found to operate reliably and provide reproducible results. Detailed magnetometry can be performed on as little as 0.5 mg of magnetite in a rat's lungs.

A Wright dust feeder produces a suitable aerosol of a commercial magnetite dust. The aerosol has a mass median aerodynamic diameter of 1.1 μm and a geometric standard deviation of 1.5.

During preliminary work with magnetite powder which had been collected on filters or had been delivered to rat lungs by intratracheal instillation or inhalation, it was found that the specific magnetization of the dust (magnetic signal per mass of dust) depends on its degree of agglomeration. Bulk dust and dust collected in a thick layer on a filter produced a signal of 0.8 nT/mg whereas a

similar mass of dust in rat lungs or collected in small amounts on ten filters produced a signal of 0.5 nT/mg. The importance of this effect will be monitored by performing both magnetic and chemical measurements of magnetite dust in animal lungs at sacrifice.

In a preliminary test of the system, magnetite dust (nominally 1 mg) was instilled into the lungs of three rats and magnetometry was performed over a period of 30 days. As expected, a portion of the magnetic signal decreased ("relaxed") during the 15-minute measurement period following magnetization of the dust in the lung field. The fraction which relaxes is often assumed to be material in mobile cells. Within one hour after instillation, the fraction which relaxed was just over one-half of the total magnetic signal. This fraction decreased slowly over a period of 30 days with a half-time in the range of normal alveolar clearance half-times for rats. The non-relaxing fraction cleared almost completely within 2 days. These preliminary data indicate that the potential for magnetometry to obtain detailed information noninvasively and repeatedly in the same animal has been realized in the systems developed for use in this project.

Pharmacomechanical Hyperresponsiveness in Ozone-Induced Airway Injury

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

Program Area: *Occupational Lung Diseases*
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Importance to Occupational Safety and Health

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

Objectives

Increased bronchial irritability (bronchial hyperreactivity) is a characteristic feature of asthma, and understanding its pathogenesis may provide new insights for better treatment. In guinea pigs with acute 03-induced airway injury, we have found cholinergic hyperreactivity which may be related to a lipooxygenase product, possibly, elaboration. Our recent studies have suggested that smooth muscle from oxidant-injured airways manifests hyperresponsiveness *in vitro* to various bronchoconstrictors, including substance P. We investigated whether this tachykinin responsiveness after oxidant exposure was caused by airway neutral endopeptidase inactivation.

Methodology

To test whether ozone-induced respiratory injury in guinea pigs was associated with inactivation of airway NEP and an increased 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. The effective dose (in μg) that produced a doubling of baseline sRaw (ED200SP) was determined by interpolation of cumulative substance P dose-response curves. NEP activity was measured in tracheal homogenates made from each animal of other groups exposed to either ozone or room air. By reverse phase, high pressure liquid chromatography, this activity was characterized by the phosphoramidon- inhibitable cleavage of alanine-p-nitroaniline from succinyl-(Ala)3-p-nitroaniline in the presence of 100 μM amastatin.

As are the cilia on respiratory mucosal epithelial cell membranes, neutral endopeptidase (NEP) may be particularly vulnerable to airway luminal oxidant injury. For the hyperreactivity accompanying some airway disorders, corticosteroid treatment is beneficial. Its effect on ozone-induced airway disease, however, is uncertain. Therefore, we 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 (3ppm for 2 h) 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 (2 mg/kg IM qd). The amount of IV SP, IV ACh, or inhaled capsaicin necessary to increase baseline specific airway resistance by 100% (ED_{200}ACh or ED_{200}SP) or 35% (ED_{135}CAP), was determined by interpolation from dose-response curves.

We have recently 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 subcellular 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 and penicillin-streptomycin, were exposed *in situ* for 5 min to 100 μM HOCl in a phosphate buffered saline solution (PBS; pH 7.0 at 37°C) or to PBS alone. Thereafter, cells were rinsed and assayed for NEP activity employing reverse phase, high pressure liquid chromatography. This activity was characterized by the generation of phosphoramidoninhibitable product (ANA) cleaved from the synthetic substrate succinyl-(ala)3-p-nitroaniline during a 30 min incubation at 37°C. 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.

Hypochlorous acid (HOCl) exposure of whole Calu-1 cells *in situ* leads to a relatively rapid and substantial decrease in whole cell NEP activity. This decrease in activity of the membrane fraction caused by HOCl is accompanied by a commensurate increase in the cytoplasmic fraction, suggesting that HOCl induces internalization of NEP from plasma membrane surfaces. To confirm this, and to assess the time course of changes in cell NEP after oxidant exposure and the potential influence of corticosteroid treatment on these, we evaluated Calu-1 NEP activity and NEP-specific mRNA over the ensuing 48 h post-HOCl in the presence or absence of 1 μM dexamethasone. Cells, grown to confluency in Dulbecco's modified eagle medium with 10% fetal bovine serum and penicillin-streptomycin, were exposed *in situ* for 5 min to 100 μM HOCl in a phosphate buffered saline solution (PBS, pH 7.0 at 37°C) or to PBS alone. Prior to exposure, some cell plates were cooled to 4°C and/or 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 thereafter. NEP activity was assayed employing reverse phase, high pressure liquid chromatography. In some experiments, post-HOCl changes in NEP-specific mRNA in the presence or absence of dexamethasone were also evaluated employing Northern blot analysis.

Significant Findings

Mean values of the changes in log ED_{200}SP were 0.27 ± 0.07 (mean ± SEM) for the ozone-exposed group and 0.08 ± 0.04 for the air-exposed group. We found that phosphoramidon significantly increased substance P reactivity in the air-exposed animals ($p<0.01$), 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: mean values were 1.81 ± 0.19 nmoles/min/mg protein for the ozone-exposed group and 2.51 ± 0.24 for air-exposed animals ($p<0.05$). 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. Our data indicate that ozone exposure decreases airway NEP activity and increases substance P reactivity which can be reversed by aerosolized NEP.

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 logEDs of the pretreated group were 0.18±0.03 (mean ± SE) for SP and 2.20±.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-zone: 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 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=S). We conclude 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.

We found that a 5 min exposure to HOCl decreased whole cell NEP activity from 74.1±4.4 (mean ± SE) to 54.3±6.0 pmoles of ANA/min/10^6 cells ($p<0.05$) while no parameter of cell viability was affected. NEP activity in the crude membrane fraction decreased 36.3±3.1% after exposure ($p<0.01$), whereas NEP activity in the soluble fraction increased 4.0±0.6%. Isolated membrane NEP exposed by itself was not affected. Subsequent experiments with reducing agents demonstrated that NEP activity of cell cultures pretreated with 100 mM of either beta-mercaptoethanol or dithiothrietol before HOCl exposure was not significantly different from control values. We conclude that whole cell HOCl exposure decreases Calu-1 plasma membrane NEP. This loss appears to occur by internalization of cell membrane NEP.

We found that sodium azide at 4°C totally blocked the effect of HOCl on Calu-1 NEP (n=6). 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 μM dexamethasone. Furthermore, dexamethasone increased NEP activity 70.1±14.1% and 267.4± 28.8% at 24 and 48 hours after HOCI exposure, respectively, compared to the untreated cells ($p<0.01$ and n=6 for each). Northern blot analysis indicated that NEP-specific mRNA did not change during spontaneous recovery, but was increased by dexamethasone 24 h post-HOCl. We conclude 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.

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Inhaled Toxic Agents: An Evaluation of Dose

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

Program Area: *Occupational Lung Diseases*
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Importance to Occupational Safety and Health

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

Objectives

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

Methodology

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

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

Significant Findings

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

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

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

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The Immunopathogenesis of Occupational Diseases Due to Reactive Chemicals

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

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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. A prior study showed that most workers with TDI asthma exhibited *in vitro* cellular responses after stimulation with specific TDI-HSA antigens, suggesting that cellular immunity may play a significant pathogenic role. Thus, it was postulated that specific *in vivo* cellular immune responses to diisocyanates in sensitized workers could result in production of cytokine mediators that could activate responder cell populations, (i.e., basophils, mast cells) to release bioactive mediators (i.e., histamine). Refinement of *in vivo* laboratory methods that measure cellular responses to specific occupational antigens could allow development of assays which could identify symptomatic workers or workers at potential risk for development of occupational immunologic diseases. These results would possibly be more sensitive than currently available *in vitro* methods that measure specific IgG and IgE responses to these chemical antigens.

Objectives

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

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

Methodology

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

Significant Findings

During the 3 years of this project, 19 diisocyanate workers have been recruited and screened for the study. Eleven 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. Of 11 symptomatic workers studied, histamine releasing factor activity in response to diisocyanate HSA conjugates was evaluable in 6 workers, 5 of whom had positive specific provocation tests to diisocyanates. In 5 of the latter 6 symptomatic workers who exhibited significant

HRF activity, cross sensitivity to other diisocyanate-HSA antigens was demonstrated. In contrast, to 5/6 symptomatic diisocyanate workers with HRF, only 1/8 of asymptomatic exposed workers exhibited specific HRF activity ($p < .05$). A leukocyte inhibitory factor assay was performed in all 11 workers who reported symptoms. Five workers exhibited significant inhibitory responses in response to diisocyanate HSA antigens. Among 6 subjects in whom results were evaluable for the both LIF and HRF assays, 3 exhibited concordance (positive responses to both assays) and 3 had discordant results. *In vivo* skin testing performed with HSA conjugates of TDI, MDI, and HDI were negative in all 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 of 6 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.

Effects of Zinc Oxide Welding Fume Inhalation

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

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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 are unknown. Recent animal and limited human data indicating that zinc oxide fume inhalation results in marked pulmonary inflammation suggest that the lung may be more than merely a conduit for exposure, but may instead play 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 IL-1 and TNF.

Significant Findings

We have carried out welding challenge exposures in 20 volunteer subjects. In nine subjects we performed late (20-22 hour) post-welding follow-up venipuncture, pulmonary function testing and bronchoscopy; in the remaining eleven subjects we performed early (6-8 hour) post-welding challenge follow-up testing. We have completed and published analysis of the first 14 subjects (5 early and 9 in the late follow-up groups). The mean cumulative zinc oxide exposure for the 14 subjects was 2.3 ± 1.7 gmin/m^3. Mean exposure was not statistically different for the early follow-up (1.8 ± 1.1 gmin/m^3, range 0.6 to 3.3 gmin/m^3) as compared to the late follow-up group (2.6 ± 1.6 gmin/m^3, range 0.6 to 5.1 gmin/m^3). 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. Although cadmium free rods were used, trace cadmium was present in seven personal breathing zone air filter samples, with a maximum level of 0.02 mg/m^3 detected in any sample. Peak copper in any sample was 0.04 mg/m^3; magnesium was detected in only 2 samples (1 mg/m^3 and 0.05 mg/m^3). Cobalt was below the level of detection (0.006 mg/m^3) in all samples. We measured ozone measured at several points during the exposures of four subjects, detecting peak values of 0.017, 0.032, 0.028, and 0.04 parts per million respectively. Nitrogen dioxide levels measured at the end of welding for three subjects were 0.8, 0.5, and 3.0 parts per million.

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% ± 18% (range 19 to 63%). There was a strongly positive correlation between cumulative zinc oxide welding fume exposure and polymorphonuclear leukocyte, macrophage, and lymphocyte concentrations in the late follow-up group. A statistically significant correlation with zinc oxide exposure could be demonstrated for polymorphonuclear leukocytes but not macrophages or total lymphocytes in the early follow-up group. The mean proportion of polymorphonuclear leukocytes among the early follow-up group was 9% ± 8% (range 2 to 21%). This proportion was statistically less than that of the late group ($p=0.005$). The mean absolute increase in blood polymorphonuclear leukocytes among the late follow-up group was 4.9 ± 2.4 x $10^3/mm^3$ (eight subjects only) and was statistically significant (95% CI 2.6 to 7.2 x $10^3/mm^3$). There was also an increase in peripheral polymorphonuclear leukocytes among the early follow-up group of 1.4 ± 2.5 x $10^3/mm^3$, although this change was not statistically significant (95% CI -1.7 to 4.4 x $10^3/mm^3$). Cumulative zinc dose was significantly correlated with the increase in peripheral polymorphonuclear leukocytes in the late follow-up group ($r = 0.77$; $p = 0.02$). We were unable to detect TNF by ELISA in the supernatant of any of the 14 bronchoalveolar lavage fluid samples. We detected trace interleukin-1 by ELISA in two of supernatant samples only.

Our data have demonstrated that zinc oxide welding fume inhalation is associated with a dose-dependent, marked inflammatory response in the lung whether or not clinical symptoms of metal fume fever were reported. Although we were unable to identify elevated interleukin-1 or TNF in the bronchoalveolar lavage fluid of our subjects at either six or 20 hours following exposure, we cannot exclude the possibility that evanescent low levels were missed. We intend further cytokine analysis, including repeat, more sensitive assays of interleukin-1 and TNF, as well as interleukin-8 and interleukin-6, two other inflammatory cytokines. We also intend to include study of subjects with follow-up 3 hours after welding fume exposure in order to evaluate responses in the first hours after zinc oxide inhalation.

Publications

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Asbestos-Induced Pleural Fibrosis and Lung Restriction

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

Program Area: *Occupational Lung Diseases*
Grant Number: *5 K01 OH00093-02*
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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 subradiographic inflammation and fibrosis of the lung parenchyma. These findings lead us to hypothesize that more sensitive indicators of parenchymal injury will allow us to fully understand the determinants of restrictive lung function in persons with asbestos-induced pleural fibrosis. The hypotheses put forth in this proposal are designed to investigate the accuracy of the diagnostic criteria established by the 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 used 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 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 type of pleural fibrosis - circumscribed pleural plaque or diffuse pleural thickening) and both force 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 further assess the clinical significance of asbestos-induced pleural fibrosis, we reconstructed images from the high resolution CT (HRCT) scan to identify and quantify the three dimensional (3D) characteristics of pleural fibrosis. We have analyzed full chest HRCT scans from 36 asbestos-exposed subjects who were on average 60 years of age and had extensive occupational exposure to asbestos. The lung volume and volume of asbestos-induced pleural disease was computed from the 3D reconstructed image of the lung. Importantly, the 3D reconstructed, computer-derived estimate of lung volume was found to correlate with the measured total lung capacity (TLC) (regression $R^2=.24$; $P=0.002$). In comparison to the chest x-ray, the images from the HRCT scan correctly identified 81% (sensitivity) of those with pleural fibrosis and correctly identified 87% (specificity) of those with normal pleura. Of the 21 subjects with abnormal pleural on the HRCT images, pleural fibrosis accounted for between 0.1% and 5.5% of the total chest cavity. Importantly, the volumetric percentage of pleural fibrosis was found to be strongly associated with restrictive lung function. In fact, after controlling for the presence of interstitial fibrosis, the percentage of pleural fibrosis identified on the 3D reconstructed image was strongly associated with the percent predicted TLC (regression coefficient = -4.6; $P=0.04$) and accounted for 13% 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. More importantly, these data demonstrate the potential utility of computer-assisted methods to estimate the extent of asbestos-induced pleural fibrosis.

Thus far, we have performed exercise ergometry on approximately eighty patients with asbestos-induced lung disease. In addition, we have worked out the methodology to perform lung compliance measures on 40 of these study subjects. During the next year, we plan to analyze the exercise and lung compliance data.

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Immuno-Epidemiology of Crab-Induced Occupational Asthma

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

Program Area: *Occupational Lung Diseases*
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Importance to Occupational Safety and Health

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

Objectives

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

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

Methodology

Based on an enumeration of all crab pickers employed for at least one day between January 1, 1986 and December 31, 1989, samples of active employees and former employees were invited to participate in this study. All participants were interviewed to determine relevant health history, and skin tested for allergies, including negative and positive controls, for common environmental allergens, as well as three different crab preparations. Skin tests were applied to the inside surfaces of both forearms prior to interview, and the test results recorded 20 minutes later. Data analysis will determine prevalences of self-reported health outcomes among current workers, which will be compared with those among former workers, to determine the role of adverse health events in leaving the industry prior to retirement.

Significant Findings

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

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

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

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

Publications

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Development of a Model for Prediction of Optimal Lifting Motion

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

Program Area: *Musculoskeletal Injuries*
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Importance to Occupational Safety and Health

Back injuries are a serious problem in terms of human suffering and cost to workers and their employers. An ergonomic approach to solve the problem is to redesign the task to fit human capabilities. For such an approach, human motion patterns under different lifting tasks should be understood. Biomechanical analyses serve a useful purpose in analyzing the motion patterns and estimating the stresses on the musculoskeletal system, especially the lumbar spine. However, the collection of displacement-time data is a tedious process in biomechanical analysis. These data collection must be made for all task combinations to be studied prior to the analysis. Such data collection requires specialized equipment and trained personnel. With the development of simulation models, it would be possible to provide means of performing the analysis without collecting the displacement-time information. Thus, the importance of this research is using simulation to estimate the kinematics and kinetics of lifting movement under several conditions of lift, range, container size, and load lifted.

Objectives

The objective of this study was to simulate the angular movement of five human joints based on the invariant characteristics of manual lifting that are multidirectional and multiarticular and executed by large muscle groups generating within maximum torques. With few exceptions, simulation of human body motion is a multidisciplinary activity. It requires combining information from the biomechanical and psychophysical approaches of ergonomics with knowledge of behavioral sciences. This study did not attempt to apply all the varied knowledge in the general field of biomechanics. Rather, it dealt with only one set of performance limitations of manual lifting - those produced by the understanding of human physical capacities and task requirements. Therefore, this study characterized the angular displacement at each joint associated with such a performance, including the extent of the movement simulated. The magnitude of the torque of each joint was predicted for each time increment (stage) of the lifting motion. Model constraints were limitations imposed by characteristics of the human body, characteristics of the task, and characteristics of the work place.

Methodology

This study was conducted to examine the hypothesis that an individual performs a lift following the principle of minimizing certain objective function while, simultaneously, the motion pattern to perform the task was subject to a set of constraints. In order to accomplish the objective of this study, the research procedure was divided into the following three phases.

1. Phase I - Pre-model development analysis: Laboratory experimental efforts were employed for the purposes of (1) generating a lifting displacement time relationship and (2) collecting dynamic joint-strength values. Specifically, extensive lifting performance data were collected to generate angular displacement time relationships at five major joints, namely, the elbow, the shoulder, the hip, the knee, the ankle. These relationships were used to estimate the ranges of joint motion (ROM), the ranges of joint angular velocities, angular accelerations, and rates of change of angular acceleration for lifting activities to be used in the formulation of the mathematical model.
2. Phase II - Model development: An optimization model was developed to generate lifting trajectories. The model was presented as a non-linear, programming problem with a non-linear objective function subject to linear, as well as non-linear constraints. As such, this model explicitly considered the minimization of a biomechanical criterion, such as the time integral of the sum of the square of the active state of the musculoskeletal system - the ratios of predicted joint moments, during the lift, to the corresponding joint moments generated under maximum exertion. The constraints included the ranges of movement (ROM) of joints, the ranges of joint angular accelerations, the ranges of rate of change of angular accelerations, and the limits of moments at the

five selected joints. The inputs for the model included the initial and final joint positions, the subjects weight and height, the time to perform the lift, the range of lift, the container size, and the weight of the container. The output was the displacement time relationship of the five selected joint angles. To find the optimal displacement-time relationship efficiently, three different search algorithms were applied: (1) Heuristic Dynamic Programming; (2) Nonlinear programming by General Reduced Gradient Algorithm; and (3) Filtering Technique by Total Enumeration.

3. Phase III - Model validation: During this phase, lifting tasks were simulated using the developed model. A verification procedure was conducted to justify the homogeneity (similarity) between the experimental (measured) trajectory of the joint and the corresponding trajectory generated by the model. This was done in terms of both trend and closeness of two behaviors while subjected to different task variables. The measure of overall predictive accuracy was the Theil's coefficient of inequality.

Significant Findings

The biomechanical simulation lifting model developed by this research can be used to evaluate the kinematics and kinetics of the lifting motion without actual data recording. The optimal lifting motion pattern, based on the time integral of the sum of the square of the ratios of predicted joint moments to the corresponding maximal joint moments, is very similar to actual motion pattern in closeness and trend of the displacement-time relation. The subjects use the minimization principle (the objective function) to certain extent. In general, the model prediction and the actual path are much similar when heavier load and higher ranges of lift are used, ie. when task is more demanding. The constraints set also play a very important role in the simulation. Any variation of the kinematic and kinetic constraints due to individual and task differences can cause significant change of the motion pattern prediction.

Publications

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Back Injuries in Municipal Employees

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

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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

Data collection was completed for the study's 200 cases and 400 controls during the period, March 1, 1990 through April 30, 1991. Cases were identified by the study coordinator in the Occupational Medicine Clinic through the collection of injury reports, clinic slips, 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 interviews.

A 10% sample of cases had a site visit to verify the ergonomic data collected by interview. Site visit and interview data are being compared.

The data from each of the specific components of the interview are being analyzed. The specific components and variables include: psychosocial, work history, history of back pain and history of injuries, ergonomic factors, health factors, and medical conditions. Significant variables from each of the specific components will be combined in subsequent analyses to identify risk factors associated with low back injury.

Significant Findings

None to date.

Ergonomic Injury Control in High Frequency Lifting Tasks

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

Program Area: *Musculoskeletal Injuries*
Grant Number: *3 R01 OH02591-02S1*
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Funding Level: *$113,781 ($205,856 Cum)*

Importance to Occupational Safety and Health

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

Objectives

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

Methodology

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

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

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

lifting technique in an environmentally controlled laboratory. A mechanical device automatically lowers the box after each lift.

Significant Findings

The conclusions drawn from the results of this study are:

1. The endurance time of individuals decreased with the increase of the frequency of lift and the amount of load lifted.
2. The highest endurance time values were recorded for the table to shoulder lifting height, while the shoulder to reach height had the lowest endurance time values. The floor to table lifting height endurance time values were somewhat lower than those for the table to shoulder lifting height.
3. Endurance time was not affected by the age of the subjects for table to shoulder and shoulder to reach lifting heights. However age had a significant effect on endurance time for the floor to table lifting height.
4. Heart rate, oxygen consumption, and the ratings of perceived exertion were not affected by age of the subjects for any of the lifting heights investigated.
5. A physiological fatigue limit (PFL), oxygen consumption, or heart rate for manual lifting tasks cannot be based on a single value as currently reported in the literature; it should be dependent on the lifting task parameters. PFLs increase with the increase of the frequency of lift and the amount of load lifted.
6. The average endurance time across all loads and frequencies for floor to table lifting height was 319 minutes (5.3 hrs). For the table to shoulder lifting height, an average endurance time of 372 minutes (6.2 hrs). The overall average endurance time for the shoulder to reach height was 275 minutes (4.6 hrs).
7. For work outputs less than 80 kg/min, it is less taxing physiologically to lift heavier loads at low frequencies than to lift lighter loads of high frequencies without affecting endurance time. For work outputs higher than 120 kg/min, there is no significant difference between lifting heavier loads at low frequencies and lifting lighter loads at high frequencies in terms of the physiological cost.
8. The correlation coefficients between overall ratings of perceived exertion and heart rate obtained in this study for prolonged lifting tasks are less than those reported in the literature for lifting tasks of short durations. This suggests that local muscle fatigue dominates the variation in the overall perception of exertion in a lifting task of prolonged duration rather than the cardiovascular strain.
9. None of the lifting frequencies studied could be sustained for an eight-hour period by 99% of the subjects tested. These results are lower than the NIOSH (1981) recommended AL values for these frequencies. Also, the recommended NIOSH (1981) MPL values for occasional lifting (less than one hour) are lower than those obtained in this study for an eight-hour duration.

Publications

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Quantitative Measures of Wrist Motions

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

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Importance to Occupational Safety and Health

Cumulative trauma disorders (CTDs), also known as repetitive trauma disorders, are disorders

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

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

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

Objectives

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

Methodology

This research was implemented in three stages.

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

Significant Findings

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

Publications

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Unexpected Trunk Loading Following Seated Vibration

David G. Wilder, Ph.D.
The University of Vermont
Department of Orthopaedics
and Rehabilitation
Given Building #4
Burlington, Vermont 05405-0068

Program Area: *Musculoskeletal Injuries*
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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 one-hour load intervention [seated vertical vibration, seated lateral vibration, seated lateral and vertical vibration, sitting still (as a control) or lying supine (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 one hour. 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, sitting still (as a control) or lying supine (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, sitting still (as a control) or lying supine (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 and reclining postures on the trunk's neuromuscular control system. The overall goal is to establish the mechanical effect of load history on the lower back and to determine whether load history increases the likelihood of significant mechanical derangement following a sudden mechanical overload. This will begin to establish whether the International Standards Organization vibration exposure criteria are reasonable limits for minimizing mechanical changes in the lumbar region.

Methodology

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

Significant Findings

None to date.

Quantitative Assessment of Carpal Tunnel Syndrome

Fredric E. Gerr, M.D.
Emory University
School of Public Health
Division of Environmental
and Occupational Health
1599 Clifton Road
Atlanta, Georgia 30329

Program Area: *Musculoskeletal Injuries*
Grant Number: *7 K01 OH00098-02*
Start & End Dates: *09/28/90 - 09/27/93*
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Importance to Occupational Safety and Health

Carpal tunnel syndrome is a common nerve entrapment disorder. It is universally accepted that it is the clinical concomitant of median nerve entrapment at the carpal canal. At this time, increasing evidence indicates that occupational factors, especially force and repetition, are etiologically related to its development. Other factors, such as awkward postures and vibration, have also been considered possible occupational etiologies, although the evidence relating these factors to the disorder is not as clear as for force and repetition.

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

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

Objectives

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

Methodology

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

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

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

Significant Findings

A statistically significant monotonic association between graded physical examination of vibration perception and vibrotactile threshold was observed for all digits tested in the upper and lower extremities. Statistically significant associations were also observed between vibrotactile thresholds and a variety of electrophysiological measures of the median, ulnar, tibial, peroneal and sural nerves. The strongest associations were observed between great toe vibrotactile thresholds and late response latencies measured in nerves in the lower extremities.

Publications

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Characterization of Posture, Force and Repetitive Motion

Robert G. Radwin, Ph.D.
University of Wisconsin, Madison
College of Engineering
Department of Industrial Engineering
1513 University Avenue
Madison, Wisconsin 53706

Program Area: *Musculoskeletal Injuries*
Grant Number: *1 K01 OH00107-01*
Start & End Dates: *09/01/91 - 08/31/94*
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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. 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

- A practical instrumentation system is being implemented for continuously measuring wrist posture and hand force. Use of spectral analysis is

being investigated for characterizing task repetitiveness, forcefulness, and postural stress. Data is transformed into the frequency domain for determining the frequency and magnitude of repetitive motion and forceful exertions performed during manual work. 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

None to date.

Biomechanical Assessment of Work Tasks and Musculature

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

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

Importance to Occupational Safety and Health

Workers engaged in lifting tasks often injure or strain their lower back musculature either acutely by attempting to lift too much or chronically due to muscle fatigue. These injuries lead to loss of productive work days to the employer as well as pain and inconvenience to the worker. In order to circumvent these injuries, preliminary research has been conducted on normal healthy subjects to determine the relationship between an individual's maximum lumbar extension strength and the torque at the lumbosacral joint (L5S1 torque) predicted through kinetic analysis during lifting. By proving the usefulness of this multi-faceted functional assessment design with normal healthy subjects, the same method could then be used to either assign workers to tasks appropriate for their strength and mechanical techniques or monitor the rehabilitation of the injured worker and expedite their return to work under defined lifting limitations.

Objectives

The aims of this investigation were to predict an individual's maximum lifting capability through information on the individual's maximum isometric lumbar extension strength and their submaximal lifting mechanics.

Methodology

Subjects (n=26) between the ages of 18 and 39 were recruited from the student body of the University of Florida and the Gainesville community. The protocol and risks were explained to all subjects and appropriate consent was obtained under the institutional research guidelines. The subjects completed three phases of testing, Phase I and II on one day and Phase III on a subsequent day. Each testing phase as well as statistical analyses are described below:

Phase I. Maximum isometric strength for each subject was measured at 7 angles of trunk flexion using the MedX lumbar extension machine (MedX Corporation, Ocala, FL). Strength at each angle was defined as the average of two trials.

Phase II. Functional lifting mechanics were determined through sagittal plane 2-D kinetics using a Motion Analysis Kinematic System (LiftTraK software, Motion Analysis, Inc.; Santa Rosa, CA). Subjects were asked to squat and lift a light load (5-15 lbs) within a 18"x18" box with side mounted handles. This lift was repeated 5 consecutive times to ensure consistency and proper lifting techniques. The mean torque value calculated by LiftTrak kinetic software for this submaximal lift was then extrapolated to develop a L5S1 torque versus "load lifted" relationship. This torque/load relationship reflects the individual's lifting mechanics. This relationship was then used to predict the maximum possible load the individual could lift based on the maximum torque generated in Phase I (MedX) and submaximal lifting mechanics (LiftTraK).

Phase III. The subjects were then asked to attempt to lift as much weight as possible 5 consecutive times using proper body mechanics. The first load attempted by the subjects was calculated as 80% of their predicted maximum load (Phase II). The weight of the lift was incrementally increased until the subject felt as if they could not lift anymore weight or their lifting mechanics were deemed improper by the physical therapist.

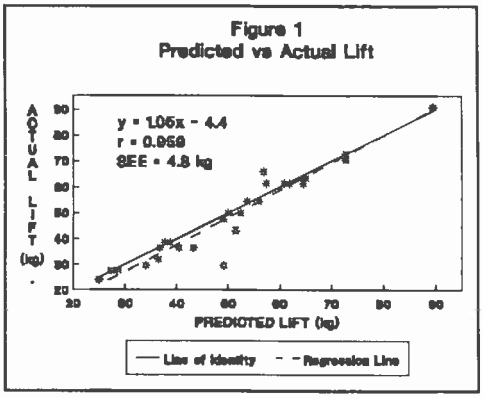
Statistics. Statistical comparisons were made between the criterion measures (actual magnitude of the maximum lift) and the predictions (estimates

of maximum lift). The statistical parameters calculated included: (1) paired Student's t-test with the significance level set at p=0.05; (2) Pearson correlation coefficient (r); (3) standard error of the estimate (SEE); and (4) total error (E).

Significant Findings

The relationship between actual load lifted and the predicted lift is illustrated in Figure 1. There was a very high correlation (r=0.959) between these parameters with very little scatter in the data about the regression line. The actual and predicted lifts were not significantly different at the p=0.05 level. Reliability statistics revealed this multi-faceted prediction method was fully capable of predicting the maximum load a subject could lift to within 10% or 11 lbs.

Further work is needed to optimize the prediction process. Strength assessment of additional muscle groups may be needed or use of a dynamic 2-D or 3-D kinetic algorithm may



improve the prediction. Ultimately, this prediction method may be beneficial to the rehabilitation of those with low back pain or it may prevent injuries by assigning appropriate activities or tasks for an individual's strength capabilities and biomechanical techniques.

Publications

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A Longitudinal Study of Musculoskeletal Disorders

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

Program Area: *Musculoskeletal Injuries*
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Start & End Dates: *08/15/89 - 08/14/91*
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Importance to Occupational Safety and Health

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

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

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

Objectives

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

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

Methodology

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

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

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

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

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

Significant Findings

In the 1983 follow-up survey, 209 workers were identified, of whom 143 had been identified in the original cross-sectional study two years earlier and 66 were new subjects. Complete or almost complete health questionnaires were obtained from 85% of the actively employed population identified in 1983, including 128 workers who had been studied at baseline, for 71.5% follow-up of the baseline population (N=179).

In each of the cross-sectional studies (1981 and 1983), over two-thirds of the subjects were stitchers. The vast majority of workers in both years were female; however, the new hires in 1983 were disproportionately male and less likely to be stitchers. The age distributions in each survey were almost identical, one-half of the subjects being from 34 to 53 years old. The total cross-sectional

population in 1983 had, on average, one year more seniority in the plant and in the industry than the population in 1981. In both years, native English-speaking workers were in the minority. Whereas in 1981 two-thirds of the study population were first- or second-generation Greek or Italian; these two ethnic groups accounted for just over one-half of all workers in 1983. The new hires were somewhat more likely to be from Latin America (Spanish-speaking) or South East Asia.

As in 1981, the hand was the most common location of musculoskeletal pain, with twice the prevalence of wrist pain and three times the frequency of elbow pain (24%, 12% and 7%, respectively). Among the total 1983 population, the prevalences of wrist and hand pain were somewhat lower than in 1981. However, among stitchers, hand pain was more frequent in 1983 than 1981; for both wrist and hand pain, the larger decreases were seen in finishers and underpressers, both jobs with larger proportions of new subjects. Also, the decreases in wrist and hand pain were concentrated in the lowest seniority stratum.

For those workers who had been surveyed in both, the 24-month cumulative incidence of new, "persistent," upper extremity pain was estimated among those workers who were pain-free at baseline. The two-year incidence rate was highest for hand pain (15%); it was 10% for forearm/elbow pain, and 7% for wrist pain. There was an increasing trend in the cumulative incidence of hand pain with increasing seniority (both plant or industry), although based on a total of only 11 new cases. A similar trend was observed in the cumulative incidence of wrist pain with industry seniority but not with seniority in the plant.

Among the workers who reported "persistent" pain at baseline, the two-year persistence of hand pain was much higher (56%) than for wrist (32%) or elbow (17%) pain. Pain defined as "non-persistent" at baseline (by frequency and duration of symptoms in the preceding year) was very unlikely to persist with increased seniority in plant or industry; there was a similar but weaker trend in the persistence of wrist pain.

Both the onset of new hand pain and the persistence of old hand pain was more common among stitchers. The cumulative incidence of hand pain was 20% in stitchers, compared with 15% overall. The persistence of hand pain from baseline was 65% in stitchers, compared with 56% overall. No such excess was observed for wrist pain. The one continuing case of elbow pain was a stitcher.

Follow-up with adequate health information was obtained for 56 (70%) of the workers with persistent pain at baseline and 72 (73%) of those without persistent pain at baseline. These proportions differed little between men and women, among job categories, or by location of symptoms. Workers with persistent shoulder or elbow pain were somewhat more likely to be lost to follow-up than those with pain at other locations.

Kinematics and Kinetics of the Pull Phase of Lifting

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

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Importance to Occupational Safety and Health

The National Institute for Occupational Safety and Health Lifting Guide (NIOSH, 1981, p. 40) states that "dynamic forces imparted by rapid or jerky motions can multiply the load's effect greatly," and recommends that manual materials handlers lift the load in a smooth and deliberate manner. However, it was suspected that the human operator must lift in a manner which causes peak forces applied by the hand to the load, resulting from a jerking motion, to overcome the inertia of the box resting on the ground. Therefore, smooth and controlled lifting motion may not be a realistic recommendation. Further, the magnitudes and time history of the hand forces are not currently known in detail. This information is necessary to advance biomechanical studies of lifting to account for the peak hand forces applied to the load. The application of knowledge of the peak applied forces is useful for biomechanical re-evaluation of lifting tasks, and for the establishment of the point of time in the lift and associated posture when L5/S1 compression and shear forces may limit lifting capacity.

Objectives

The first objective of the research was to directly measure applied forces by the hands to a load lifted from floor to knuckle height, and compare these to calculations of hand forces by an

existing dynamic biomechanical model, such as Dynalift. The second objective was to determine the effects of speed of lifting motion, frequency, and load on the peak hand forces during the lift.

Methodology

A container with handles was designed which measured the vertical and fore-aft forces applied by the lifter on the container using strain gages mounted on the handles. This system was calibrated prior to use in the experiment. Five male subjects were used in the experiment. Each subject participated in a task familiarization period (two days, two hours/day). The experimental design was a split plot design using subjects as blocks. The independent variables were lifting speeds (two levels), lifting frequency (three levels), load lifted in terms of MAWL (three levels), and weight (five levels). Dependent variables selected were magnitude of the peak vertical and fore-aft hand forces and maximum compressive and shear forces on L5/S1.

Significant Findings

The measured peak hand forces were consistently greater than the modeled hand forces. Differences between the measured and modeled forces were significant for vertical and fore-aft forces at normal and fast speeds of lift, with the differences greater for fast speed of lift than for normal speed of lift. A sudden peak magnitude of hand forces was exhibited in most lifting trials. The spike was evident immediately near liftoff, usually within .07 seconds of liftoff. In most lifts, the peak hand forces surpassed the model forces, but then dropped below or matched the modeled forces. In general the model appears to account for external forces applied to the load after the load has been picked up. However, at the pull phase, the model significantly underestimated the hand forces applied to the load for both normal and fast speeds of lift.

The calculated peak compression L5/S1 forces using measured applied hand forces as input were 3 to 10% greater than the model calculated forces. The small differences between the peak L5/S1 compression forces calculated with measured forces were not significant for the normal speed of lift. However, at fast speeds of lift, peak L5/S1 compressions were highly significantly different (ranging from 104 to 111% of modeled) between modeled and modeled with measured input conditions. The differences between peak L5/S1 shear forces ranged from 108 to 136% of the modeled values and were significant for fast and normal speeds of lift.

Data also demonstrated that peak L5/S1 compression forces above 6370 N occurred at light loads of 6.25 and 10.91 kg lifted at fast speed, and 15.45 kg lifted at normal speed. The mean peak compression force for all lifting tasks at fast lifting speed were greater than 6370 N, and all lifts executed at normal speed caused forces greater than 6370 N except 35% MAWL loads.

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Occupational Epidemiology of Carpal Tunnel Syndrome

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

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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. The

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

Objectives

The primary objective of this research is to provide epidemiologic information regarding the prevalence of CTS among occupational groups for which there is a paucity of epidemiologic data. In addition to examining occupational factors associated with CTS prevalence, other objectives 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 4,000 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 obtained in the cross-sectional survey questionnaire and data that will be collected in 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 will also receive electrodiagnostic testing (distal sensory and motor latencies of the median nerve), clinical exams (Phalen's test, Tinel's test, and measurements of wrist size and dimensions), and a personal interview. The case-control interview includes more extensive questions on CTS symptoms, medical history, and occupational work task information. Cases are selected on the basis of their reporting of CTS symptoms in the cross-sectional survey; controls will be selected among those who do not report nocturnal pain or symptoms localized in the distribution area of the median nerve. Controls will be matched to cases by age, sex, and occupation.

Significant Findings

Cross-sectional survey data are currently available, and some preliminary analyses have been completed. Case-control data collection will begin in January 1992 and should be finished by July 1992. Prevalence rates for CTS symptoms (the presence of pain, tingling, and numbness in the median nerve area) are 21.3% for Local 660 members (office workers), 17.3% for Local 709 members (sprinkler fitters), and 16.6% for Local 409 members (carpenters). The prevalence rates decrease substantially (to 7.5-9.0%) when the presence of night symptoms is included in a CTS symptoms definition. 5.2% of the office workers, 4.7% of the sprinkler fitters and 5.6% of the carpenters reported a history of a medical diagnosis of carpal tunnel syndrome. Analyses are underway that examine work task demands and other important factors that may influence the occurrence of carpal tunnel syndrome.

Sudden Loading and Fatigue Effects on the Human Spine

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

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Importance to Occupational Safety and Health

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

Objectives

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

Methodology

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

The analysis involves several separate steps. The first utilizes system identification theory. This will determine the underlying dynamics for each subject's response. The second analyzes the onset times and rates of muscle activation and coactivation. The next synthesizes the results of the previous two into practical information. A minimum compression level is determined directly from the dynamics of each subject and then will be compared to some static models for similar positions and motions. Lastly, several inherent parameters will be estimated using different techniques. The results will then be compared to each other based on useability and information content.

Significant Findings

Data collection was completed in January 1992. Since then observations made from the raw data indicate that changes in response are seen between the unfatigued and fatigued conditions within each subject. Additionally, the accelerations of the torso's center of mass appear to approximate second-order impulse responses, as hypothesized.

Prevention of Cumulative Trauma Disorders

Beth Ann Marcus, Ph.D.
EXOS, Inc.
8 Blanchard Road
Burlington, Massachusetts 01803

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Importance to Occupational Safety and Health

CTDs, which have been called the "Occupational Epidemic of the 90's," are injuries that affect the hand and wrist as a result of performing repetitive tasks. OSHA predicts that by the year 2000, 50% of

the U.S. workforce will be affected by CTDs. The specific aim of the proposed research is to develop an innovative method for dealing with Cumulative Trauma Disorders (CTDs) in the workplace. Using new technology, our goal is to establish a quantitative relationship between CTDs and work conditions. The ultimate result will be the ability to:

1. identify high risk work conditions,
2. quantify the problems providing a rational means of altering these conditions, and
3. verify that the changes will indeed reduce the risks.

Thus, rather than waiting until CTDs reach a debilitating state, this technology will permit early detection and prevention.

The proposed effort is focused on validating the GripMaster™ in measuring wrist posture and grip force against other existing technologies. In addition, preliminary field tests will be conducted to identify operational parameters that will help to shape the design of a field compatible monitor. This type of monitor has enormous commercial potential in both helping to design better products and preventing injuries.

Objectives

The objective of this project is to validate the GripMaster™ by comparing it to other technologies for which there is an existing body of knowledge. In the course of this process, it is anticipated that a deeper understanding of the type of measures which are useful will be developed. With this understanding, we will identify opportunities to improve the GripMaster™ by making it easier to use, more compatible with the field environment, and by developing methods of using it and analyzing the resulting data.

Methodology

Two sets of tests will be performed: laboratory and field tests. The laboratory will be focused on validation of the techniques and measurement devices. The field testing will be a pilot study to verify that the validation holds equally for the field environment and to identify operation parameters that will affect the development of the final commercial products and test procedures. The GM sensors will be mounted on the fingers and thenar eminence of the subject and calibration will be performed with a load cell.

The preliminary field studies will be conducted at two industrial sites which have workers performing high force, high repetition, or high dexterity hand work. The preliminary selection has been made and scheduling, at a compact disc manufacturing and packaging plant and a lock manufacturer, is underway.

The protocol used in the laboratory will be adapted based upon the knowledge gained in performing the testing. It will also be simplified where possible to make the process more compatible with the factory environment.

Significant Findings

None to date.

Occupational Cancer Surveillance: New Approaches

G. Marie Swanson, Ph.D.
Michigan State University
Cancer Center
A-211 East Fee Hall
East Lansing, Michigan 48824

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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. Additionally, two analytic studies have been launched from OCISS that would not have been feasible otherwise. Both studies utilize the pool of lung cancer patients that never smoked tobacco identified by OCISS. One study is an investigation of familial risk of lung cancer; OCISS questionnaires are being utilized to obtain histories from relatives of these non-smoking lung cancer cases. The second study is evaluating household radon exposure among the non-smoking lung cancer patients. 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

Analyses performed for cancers of the lung and the urinary bladder have identified excess risk for certain occupations and industries. 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%. Additionally, we found that the risk of urinary bladder cancer due to cigarette smoking was greater among black males and females than among white males and females. A significant decrease in urinary bladder cancer risk was observed among health care professionals. Industries with elevated risk among bladder cancer patients included wood manufacturing, drug manufacturing, hardware sales, and other transportation manufacturing.

Methodologic analyses conducted have shown that when death certificate information regarding usual occupation and industry is compared with information obtained by interview for the same individual, the death certificate is in error in 30% to 50% of the cases.

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Relative Health Risks of Diesel Emission Control Systems

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

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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 and DPM and semi-volatile organics collected from a heavy-duty diesel engine operated with and without emission control devices in the laboratory. Together, these data will help evaluate the potential health effects of diesel exhaust and the impact of emission control devices on the underground mine environment.

Objectives

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

Methodology

Samples from four dieselized underground coal mines were collected by BOM personnel using Hi-volume samplers equipped with inertial impactors to collect size-differentiated particle samples. Particles ≤ 1 μm 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.

Laboratory samples for DPM and semi-volatile organics were collected at the BOM in two separate studies: (1) with and without a catalyzed diesel particle filter (CDPF); and (2) with and without an oxidation catalytic converter (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. Coal samples from each mine were also extracted and assayed for PAH levels and activity. The data from the laboratory samples were converted to estimated in-mine concentrations to better evaluate potential impacts of certain engine operating conditions and emission control systems.

Significant Findings

The overall mean haulageway DPM concentration for all mines was 1.4 mg/m^3 (28% C.V.), with a mean/mine range of 0.9-1.9 mg/m^3. The values were not significantly different between mines and represent potential maximum diesel-related emissions in the haulageway areas. These haulageway DPM concentrations were also similar to those found at the same mines using personal diesel exhaust aerosol samplers. Significant differences were found between mines for SOF concentrations (overall mine mean of 0.2 mg/m^3, 66% C.V., range of 0.08-0.4 mg/m^3). No significant differences were found in DPM-associated mutagenic activity (revertants/m^3) between mines (overall mine mean of 700 revertants/m^3, 38% C.V., range of 450-970 revertants/m^3). PAH concentrations (ng/m^3) were consistently higher (significant difference) for one of the mines. The mean fluoranthene level for all mines was 190 ng/m^3 (92% C.V., range of 48-390 ng/m^3), the mean pyrene level was 120 ng/m^3 (100% C.V., range of 32-270 ng/m^3), and the mean benzo[a]pyrene level was 26 ng/m^3 (120% C.V., range of <0.05-61 ng/m^3). The PAH concentrations and mutagenicity levels were generally within the broad ranges reported for other types of dieselized underground mines. Analysis of submicrometer coal particles indicated they would contribute little in terms of SOF, PAH or mutagenic activity. Up to 20-fold differences were found in DPM, SOF, mutagenicity, and PAH values in the intake samples at the four mines, probably due to the random operation of diesel support vehicles operating upstream from the Hi-volume samplers. The differences between the mines may be due to variations in diesel engine operation, fueling, and maintenance.

A comparison was made of the laboratory data (with no control device) to the actual values measured at the haulageway sites using an in-mine dilution ratio of 100:1. The results generally indicated no significant differences in DPM, SOF, mutagenic activity, and PAH concentrations between the laboratory and in-mine data. This indicated that laboratory diesel emissions data are useful in estimating in-mine levels.

Use of the CDPF in laboratory studies resulted in significant changes in total hydrocarbons, carbon monoxide, DPM, SOF, sulfates, XOC, mutagenic activity, and PAH concentrations. With the exception of sulfates, all these concentrations decreased (typically 290%) with CDPF use. The CDPF effects on reducing SOF or XOC-associated mutagenic activity concentrations were due to reductions in SOF or XOC as the revertants/μg values either did not change (XOC) or were increased (SOF) with CDPF use. The reductions in the vapor phase-associated concentrations (XOC and XOC-associated mutagenic activity and PAH) were typically less than the DPM-associated emissions. The more volatile PAH, e.g., fluoranthene and pyrene, were about equally partitioned between the particle and vapor phases with and without the CDPF, but the remaining PAH were found only with the particle phase and only without CDPF use. Based on these analyses,

in-mine DPM concentrations with the CDPF installed would be below 0.1 mg/m3, representing at least 10-fold reductions in DPM. Similar reductions would also be expected in DPM-associated mutagenic activity and PAH concentrations; organics, mutagenic activity, and PAH associated with the vapor phase would also be decreased, but to a lesser extent.

Reductions of 30-60% with OCC use were observed for total hydrocarbons, carbon monoxide, DPM, SOF, XOC, mutagenic activity, and PAH concentrations; all changes were found to be significant. OCC use resulted in significant changes (reductions) in SOF but not XOC-associated mutagenic activity on a mass basis (revertants/μg). Some significant differences were observed between the different fuels, particularly ones with differing aromatics contents (as determined by FIAM). Lower DPM and solids levels were found with lower aromatic levels (i.e., 11 wt.% vs. 20 wt.%). In general, higher levels of particle and vapor phase-associated mutagenic activity and of some PAH were found with the lower aromatic levels. Based on these analyses, potential in-mine reductions in DPM and other diesel emissions may not be as great with the OCC as with CDPF use, with DPM concentrations reduced to about 0.2 - 0.3 mg/m3 depending on the type of low sulfur fuel used. However, the OCC may provide advantages in terms of durability and ease of operation.

Biologic Monitoring/Risk Assessment in an Exposed Cohort

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

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

Objectives

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

Methodology

Members of a previously identified cohort of workers (N=2,005) exposed to benzidine and an equal number of unexposed controls were 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 correlate these with each other and with exogenous and endogenous risk factors to determine which best discriminate individuals and subgroups at risk for bladder cancer. Included among QFIA analyses are: DNA hyperploidy, F-actin levels in cells, labeling with an antibody against a tumor-related antigen found in low-grade tumors, and selected oncogene protein levels.

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

Significant Findings

The pilot study demonstrated that an excellent cohort is available for the study, with good compliance and participation. Adequate histories and physical and laboratory data can be collected and analyzed to determine endogenous and exogenous risk factors. Since completion of the pilot study, 745 subjects have been screened, including 610 exposed to amines and 135 nonexposed controls. Urine samples have been collected and sent to Oklahoma for processing and quantitative analysis, and others were collected for conventional cytology, Papanicolaou stained, and read in Shanghai by local cytopathologists. Hematuria testing, using a dipstick, was performed on urine samples. Blood specimens were collected from all subjects, separated and stored, at -70°C, in Beijing at the Institute of Occupational Medicine. Each subject underwent a physical examination and those with strong clinical indications of bladder cancer had urologic examination; two cases of bladder cancer were found.

Detailed plans have been made for continuing the screening, as well as clinical followup of previously screened subjects with positive Pap cytology of hematuria findings. All urinary samples sent to Oklahoma have been processed for long-term storage and analysis. The procedure was tested and all markers were found to be stable for at least six months. The prototype program for the IBAS system has been completed and can scan 5,000-10,000 cells and store images from selected abnormal cells in less time than is required for the old imaging system. We have conducted preliminary studies to identify new markers useful for evaluating individual risk. The QFIA assays will include two new markers neu and M344. The assays promise to provide additional information that can be used to define individual risk more precisely than DNA and morphology alone. Significant advances have been made in determining multiple markers on the same cell and we can now perform quantitative DNA, qualitative markers on tumor-associated antigens and quantitation of one other marker on the same cell, which will aid in further defining the sequence of events n the oncogenic process, provide a means to deal with the problem of heterogeneity and potentially improve both sensitivity and specificity of cancer detection and risk prognostication.

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Case Control Study of Cancer in Synthetic Rubber Workers

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

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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 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 lymphohematopoietic 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) 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; and (3) a characterization of exposure by jobs using measured levels of butadiene and styrene, the comparison of these measured levels to the estimated relative ranks used in earlier studies, and the use of both the actual measures and the estimated measures in the case-control study.

Significant Findings

The following results are preliminary and, although the investigators believe them to be accurate reflections of the data, results are subject to change based on further refining of outcome measures (from medical records review) and exposure assessment.

The original case-control data set was edited to eliminate some misclassification, thus resulting in better discrimination between exposed and nonexposed workers. Using the log-transformation of the lifetime estimated exposure score as a continuous variable results in an increased risk from butadiene for all lympho-hematopoietic cancers (odds ratio=1.26 for each increment in exposure; $p=0.008$). The model with only butadiene is the best of the models (compared to models using styrene alone, butadiene and styrene, and butadiene, styrene, and an interaction term). These results indicate an increasing risk with increasing exposure score of butadiene but not of styrene. There is no evidence of a statistical interaction. When using the mean of the exposure scores as a cut point to define exposure, the reanalysis shows an odds ratio of 3.3 for butadiene exposure ($p=0.004$). Results for five lag periods (2, 5, 10, 15, and 20 years) indicate there is a significant increase in risk associated with butadiene exposure for each lag period up to 15 years, but there is no increase in the magnitude of the odds ratios when presumed "extraneous" exposure is removed until 20 years of latency. Styrene, on the other hand, shows a marked increase in the apparent risk when 15 and 20 years of latency are included. Further analyses will determine whether these differences are due to differences in response to chemicals based on cancer site within the lympho-hematopoietic classification.

Hospital records for 53 of the 55 cases of lympho-hematopoietic cancers with records available showed correct classification in the lympho-hematopoietic group. The most remarkable observation from the review of these records is that many of these patients have multiple cancers of the lympho-hematopoietic system with a total of 68 identified in the 53 patients. In addition, solid tumors at other sites were found in six cases, frequently with autopsy identification of the lesion. Therefore, the cases have on average 1.4 cancers per patient, most of which are multiple lesions involving the bone marrow/immune system.

During the study period, data for short-term workers were gathered and processed. In addition, some missing birth dates and racial designations were imputed based on algorithms derived from known data in the cohort. The inclusion of short-term workers (those with less than one year of employment) in the analysis increases the all cause mortality, but remarkably does not increase the standardized mortality ratios for cancer or circulatory diseases. Almost all of the excess is accounted for by external causes of death, respiratory disease, and deaths in a residual class (no known cause because no death certificate was found). For specific cancers of interest in the current research, the long-term workers have higher risks than short-term workers. This suggests that those exposed in the industry longer have higher risk of cancer. Further examination of the differences in risks at specific sites is underway. However, the data at present indicate that inclusion of these short-term workers does not add to the risk.

Analyses of the measurements and the expert rankings show agreement between the job ranks and the exposure measures for most jobs (particularly for the highly exposed and the low exposed jobs).

Ways to address the problems in the intermediate rankings are currently under study.

Improved Magnetic Field Exposure Assessment

David Kriebel, Sc.D.
University of Lowell
College of Engineering
Department of Work Environment
One University Avenue
Lowell, Massachusetts 01854

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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 disease risk. This investigation is developing and evaluating methods for making appropriate exposure assignments to worker subjects in epidemiologic studies, and for choosing an efficient measurement strategy.

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 an accurate assessment of the degree of variability within given work locations (which is thought to be greater than for airborne hazards), and over time for a given subject.

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 metal machining and assembly plant in the midwest. 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 min averages for further analysis of between-worker and temporal variability.

The spot meter was 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 average exposure estimates could be made. Errors which might occur by relying on a spot meter to measure fields which decrease very rapidly with distance from the source can be evaluated with these data.

Significant Findings

Background exposure at this heavy industrial plant was surprisingly low, less than 0.2 milliGauss (mG). This compares with a 25th percentile home exposure 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.

Estimated average exposures, calculated from spot measurements and time estimates at several 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 working hypothesis was that electric motors would dominate, 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, it is difficult to decide how to summarize the detailed exposure records which are available from the dosimeter. For this work, six different exposure indices have been computed for each worker, reflecting several possible biologic mechanisms of harm. 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

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

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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. Preliminary 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 none in normal, healthy controls; in addition, a small percentage of lung cancer patients (<5%) exhibit point mutated forms of p21 in their serum. Furthermore, preliminary 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 suggests that serum p21 may be a useful early marker of preclinical carcinogenic pulmonary response in persons with respiratory exposure to carcinogens. Analysis of the results for other oncoproteins in relation to both malignant and non-malignant disease endpoints is continuing.

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Leukocyte DNA Adducts after Carcinogen Exposure

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

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Importance to Occupational Safety and Health

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

Objectives

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

Methodology

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

Initially, the relationship of dose of carcinogen to adduct levels in the above tissues and the time course of the appearance and disappearance of adducts in these tissues will be determined using 2-aminofluorene as a representative carcinogenic arylamine. Subsequently, representatives of other classes of carcinogens such as benzo[a]pyrene as a representative polycyclic aromatic hydrocarbon will be used.

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

Significant Findings

In mice, the formation of 2-aminofluorene-DNA adducts in the target tissues liver and bladder is dependent on a number of factors that can modify the metabolic activation of 2-aminofluorene. Among these are age at time of exposure, sex, and acetylator status. Studies of these variables have indicated that acetylator status is of major significance in hepatic DNA
adduction, while age at time of exposure is particularly important in bladder adduct formation in male mice. Sex is a significant determinant of which tissue will be the major target of DNA damage (liver in females and bladder in males). In order to simplify initial comparisons between target tissues and WBC, we have examined C57BL/6J (rapid acetylators) male mice at 7 weeks of age.

The formation and disappearance of WBC DNA adducts for 24 hr after exposure to 2-aminofluorene was measured and compared with liver and urinary bladder DNA adducts. In general, adduction of DNA by 2-AF metabolites appeared similar in the three tissues. The highest level of 2-AF-DNA adducts were observed at 3 hr and decreased with time over the period studied. The actual amount of 2-AF-DNA adducts found in WBC was about 15% of the amount found in liver and 5% of the amount found in bladder.

The early findings indicate that for acute exposures, WBC are potentially useful as monitors of arylamine carcinogen induced damage to target tissues. Further exploration of the usefulness of WBC adducts in more chronic exposures and with different carcinogens is required and currently in progress.

Susceptibility to Genetic Damage from Butadiene

Karl T. Kelsey, M.D.
Harvard School of Public Health
Occupational Health Program
665 Huntington Avenue
Boston, Massachusetts 02115

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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

A pilot study has been started in collaboration with union personnel.

Activation of H-Ras Oncogene by N-Heterocyclic Aromatics

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

Program Area: *Occupational Cancers*
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Start & End Dates: *08/01/89 - 07/31/92*
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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

Suresh P. Krishnan
University of Cincinnati
College of Medicine
Department of Environmental Health
3223 Eden Avenue
Cincinnati, Ohio 45267-0056

Program Area: *Occupational Cancers*
Grant Number: *1 R03 OH02880-01*
Start & End Dates: *09/30/91 - 09/29/93*
Funding Level: *$18,463 ($18,463 Cum)*

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 specific aims of our proposed research are as follows:

1. Determine the kinetics of DNA adduct levels (^{32}P post labeling assay) and micronuclei frequencies (cytochalasin-B blocking method) in mouse skin and liver for BaP and 4ABP separately.

2. Determine the ability of both compounds to cause chromosome damage in mouse skin and liver as measured by micronuclei frequencies.
3. Establish dose-response relationships between carcinogen-DNA adducts and cytogenetic damage as measured by micronuclei frequencies.
4. Evaluate the mechanisms for clastogenicity 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 provide us with information regarding the times of maximum binding and maximum micronuclei expression.
2. Multiple Dosing Study - This section of the 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 aseptic conditions. They will be resuspended in low calcium minimum essential medium and plated in tissue culture flasks at appropriate densities. 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 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

None to date.

Explosion Hazards Related to Combustible Dusts

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

Program Area: *Traumatic Injuries*
Grant Number: *5 R01 OH01122-09*
Start & End Dates: *01/01/81 - 03/29/92*
Funding Level: *$228,800 ($1,229,361 Cum)*

Importance to Occupational Safety and Health

The safety hazard resulting from finely divided combustible material has to some extent been recognized, although it would appear that these materials are not treated with the same concern as flammable liquids and gases. In the grain industry in fiscal 1991, there were 16 dust explosions, 9 injuries, and 1 death. It is the grain and underground coal mining industries in which dust explosions are most prevalent. This situation is much improved from the late 1970's and early 1980's, in that in FY 1987 and FY 1990 there were no deaths as compared with the high for this decade of 11 in FY 1981. Additionally, the number of injuries has declined steadily from a decade high of 59, also in FY 1981. Data collected under the research effort supported by this grant has had an influence upon safety regulations for the grain industry put into effect by OSHA on March 31, 1988 and finally upheld by the U.S. Circuit Court.

Objectives

The purpose of this research project is to quantitatively characterize the explosion hazard represented by suspended and layered combustible dust. Using specially developed facilities, measurements are made which describe the fundamental aspects of dust combustion (laminar and turbulent burning velocities, denotation, velocity, reaction zone thickness, etc.) as a function of the parameters describing the initial conditions for the dust (chemical composition, size, shape, concentration, moisture content, premixedness, turbulence parameters including intensity and scale, etc.) This contrasts strongly with the traditional characterization of dust explosion hazards which employed "standard" testing apparatus in which well characterized dust was allowed to react under unknown and in some cases inappropriate conditions and where the results were characterized by parameters which may not be quantatively useful. Analytical efforts directed at the development of models which explain the observed phenomena have been productive.

Methodology

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

combustion problem within the framework initially established by the U.S. Bureau of Mines, although this has now been significantly improved upon. For the suspended dust, much of the analysis depends upon that done by Bradley at Leeds for turbulent premixed gas flames. Modelling of dust detonations has been based upon the heterogeneous models originally developed at the University of Michigan with appropriate modifications. The modelling of particulate combustion is similar to classic droplet combustion models and that done for coal particles.

Significant Findings

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

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Reduction of Occupational Injury Deaths in Rural Colorado

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

Program Area: *Traumatic Injuries*
Grant Number: *5 R01 OH02601-03*
Start & End Dates: *09/30/88 - 11/30/91*
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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 lCHA). 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 72 in 1990 for a total of 324 deaths. The statewide death rate declined 41% from 6.1 to 3.6 per 100, 000.

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 an OSHA classification system to assign primary, indirect, and basic causes to these deaths. Indirect causes include 38 hazardous practices and 63 hazardous conditions. 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 practice conditions were identified. A similar pattern was seen with the basic cause classification which groups causes by personal factors, policies and decisions, and job/environmental factors. A combination of personal factors and either job or policy factors were seen in 57% of the cases, job/environmental factors only in 38%, and in only 15% personal factors alone were identified.

Rural/urban difference was seen only in the significantly greater number of hazardous conditions in the rural area. The two major categories of differences were workplace environmental hazards and natural hazards.

Trauma Care Effectiveness was determined by geographic area for occupational ATI fatalities and for severe nonfatal ATIs. All injury survivors and nonsurvivors were ascertained and categorized as salvageable or nonsalvageable using the Injury Severity Score (ISS) as an indicator of salvageability; ISS <75 = salvageable, ISS of 75 = nonsalvageable. Nonfatal work-related ATI were identified from the CHA Hospital Discharge data (HDD) and selected by primary payment source indicated to be workers' compensation. Using the selected WC ATI discharges, ISS 16+, the JHU software program (ICDAMAP) assigned ISS from ICD9 discharge diagnoses codes. Overall statewide trauma care effectiveness was 73%. This level of effectiveness compares favorably to that observed with the Multiple Trauma Outcome Study, suggesting that statewide trauma care is quite good. The final report will assess rural/urban difference in trauma care effectiveness. Overall assessment of the

relative importance of risk factors for occupational injury fatality and prioritization of intervention strategies will be included as part of the final report.

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The Health Hazards of Child Labor

Philip J. Landrigan, M.D.
Mount Sinai School of Medicine
Department of Community Medicine
1 Gustave L. Levy Place, Box 1057
New York, New York 10029-6574

Program Area: *Traumatic Injuries*
Grant Number: *5 R01 OH02717-02*
Start & End Dates: *12/01/89 - 11/30/91*
Funding Level: *$61,155 ($118,001 Cum)*

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.

Publications

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Case-Control Study of Sawmill Injuries in Maine

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

Program Area: *Traumatic Injuries*
Grant Number: *5 R01 OH02741-02*
Start & End Dates: *06/01/90 – 05/31/92*
Funding Level: *$64,629 ($119,282 Cum)*

Importance to Occupational Safety and Health

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

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

Objectives

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

Methodology

A case-control study is being conducted of risk factors in the work environment for occupational injury in the Maine wood products industry (SIC 242-249). A population-based, case-control study design is employed, in which cases are identified from employers' First Reports of Injury filed with the State Workers' Compensation Commission. Controls are selected from employee lists provided by 22 participating employers (about 1200 employees) or from membership lists provided by 3 participating union locals (about 800 members).

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

All subjects will be interviewed to obtain information on demographics, anthropometry, work history, and medical history. The interview also obtains information on production tasks, characteristics of the equipment, tools and product, and other features of the physical and psychosocial work environment. For cases, this information is obtained for the specific activities performed on a typical work day and at the time of the injury. Controls are asked about their work activities on a typical work day and on the last full day worked prior to the interview. 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 are also 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 have visited or 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

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

Program Area: *Traumatic Injuries*
Grant Number: *1 R01 OH02760-01*
Start & End Dates: *09/01/90 - 08/31/92*
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Importance to Occupational Safety and Health

While the Bureau of Labor Statistics regularly publishes lists of industries according to illness and injury rates, few lists of jobs are available which rank occupations by mortality and/or disability rates. This is unfortunate for two reasons. First, OSHA resources need to be targeted to not only high risk industries but high risk occupations as well. Second, the public would benefit from having greater information 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 employers of job hazards, Occupational Hazards, Vol. 53 no. 1 (Jan 1991): 45-46).

Objectives

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

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

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

The proposed study will analyze each of these 18 tables and will compare women with men; 1978-1981 with 1983-1985; deaths with permanent disabilities; and deaths with ranking of occupations by blood pressure. (Ranking occupations based

upon the blood pressures of incumbents, JOM, Vol. 33, no. 8 (Aug 1991): 853-861).

Methodology

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

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

Significant Findings

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) x 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).

Table 1
Top 20 Job - Related Male and Female Death Rates, 1979,
by 1970 U.S. Census Occupation codes

Rank	Census Code	Occupation	Rate per 100,000 employees per year
1	163	air plane pilots	115.0
2	780	miscellaneous laborers	89.5
3	550	structural metal crafts workers, iron workers	82.1
4	412	bulldozer operators	63.2
5	961	firefighters	59.2
6	433	electric power line and cable installers and repairers	57.2
7	754	garbage collectors	55.3
8	495	not specified mechanics and repairers	42.2
9	715	truck drivers	39.8
10	761	timber cutting and logging	38.3
11	640	mine operatives	35.4
12	622	furnace tenders, smelters, and pourers metal	34.4
13	965	sheriffs and bailiffs	32.8
14	751	construction laborers	31.7
15	492	miscellaneous mechanics and repairers	29.8
16	436	road machine operators, except bulldozer	27.8
17	750	carpenters helpers	26.5
18	964	police and detectives	24.0
19	402	bakers	23.7
20	932	attendants, recreation and amusement	20.9

Table 2
Cause of Female Deaths in 1980

Rank	Cause	Number of deaths
1	multiple injuries	8
2	asphyxia, strangulation	6
3	fracture	5
4	heart conditions including heart attack	5
5	cut, laceration, puncture	4
	Total	42

Table 3
Cause of Male Deaths in 1980

Rank	Cause	Number of deaths
1	multiple injuries	235
2	heart conditions, including heart attack	190
3	fracture	169
4	cut, laceration, puncture	88
5	nonclassificable	75
6	contusion, crushing, bruise	44
7	heat burn	41
8	asphyxia, strangulation	39
9	electric shock, electrocution	37
10	silicosis	29
	Total	1040

Role of Postural Stability in Industrial Falls

Amit Bhattacharya, Ph.D.
University of Cincinnati
College of Medicine
Department of Environmental Health
3223 Eden Avenue
Cincinnati, Ohio 45267-0056

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Importance to Occupational Safety and Health

In most industries, falls are the key cause of accidents in the workplace. Falls usually result in severe bodily damage, permanent disability, and even fatality. In 1988, falls were the third leading type of accident occurring in the workplace. The National Safety Council estimated that the numbers of injuries caused by occupational falls range between 250,000 and 300,000 per year. In 1987, falls at the job site were responsible for about 16.4% of occupational fatalities in the United States. 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. In an analysis of accident profiles among New York industries,

previous investigators have found that the following professions showed high risk of fall accidents: roofers, painters and decorators, carpenters, masons, electricians, office and service workers, hospital workers, and sheet metal workers. 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.

The proposed 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 (described by postural sway parameters and IPSB) 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 broken bones, spinal injuries, fatalities, permanent 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 different workloads, standing surface contamination conditions and firmness, lighting, and peripheral vision conditions.
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 workloads, standing surface contamination condition and firmness, peripheral vision conditions, and lighting.
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 workload, standing surface contamination conditions and firmness, lighting, and peripheral vision conditions.

Methodology

In the proposed study, postural instability and fall potential of risk factors will be evaluated for 100 industrial workers' performance (21 to 55 years of age) on 32 test conditions which represent combinations of these risk factors. These tests simulate conditions which occur in industrial/occupational environments. Subjects will be tested immediately after exposure to light and moderate-to-heavy workloads (bicycle ergometer) to quantitate their postural stability while standing on surfaces with different contamination conditions and firmness. Their peripheral vision and the environmental lighting conditions will also be varied. Each subject will undergo the 32 tests, comprised of each of 32 possible treatment combinations among the four risk factors (conditions) and two workloads. Condition 1 will be standing on dry or oily surface. Condition 2 will be "acceptable, good" or "unacceptable, poor" environmental lighting. Condition 3 will be blocked or unblocked peripheral vision, and Condition 4 will be standing on firm or compliant surface. Before and immediately after completion of a workload, the subject will be 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 will be assessed immediately after each test using a subjective Scale of Rating of Perceived Sense of Fall. The postural stability will be measured with a six-component force platform. Each subject's "Functional Stability Boundary" will be determined. This information will be used for the calculation of the Index of Proximity to Stability Boundary (IPSB). The value of IPSB obtained during the postural stability tests will be 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. Postural sway parameters will be measured to investigate the age-associated differences in maintenance of upright postural

balance under all combinations of workloads and four risk factor conditions.

Significant Findings

None to date.

Workplace Assault-Related Injuries: Incidence and Risk

Jess F. Kraus, Ph.D.
University of California, Los Angeles
School of Public Health
Department of Epidemiology
10833 Le Conte Avenue
Los Angeles, California 90024-1772

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Grant Number: *1 R01 OH02872-01*
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Funding Level: *$171,886 ($171,886 Cum)*

Importance to Occupational Safety and Health

Homicide in the workplace accounted for 13 percent of 7,000 traumatic work-related deaths in the United States from 1980 through 1985. About 11 percent of deaths in males and about 42 percent of deaths in females are due to homicide. Among older workers, homicide is the leading external cause of death while at work. Work-related homicide rates are three times higher for black and Asian minorities than for whites. The occupations at highest risk (except police) are minority-dominated. Occupations with the highest homicide rates are police, taxi drivers, security guards, salespersons, waiters/waitresses, bus/truck drivers, janitors, and supervisors or proprietors of food-serving or food-selling establishments. These occupations account for about 15 percent (in 1980) of the work force in California, and perhaps, the United States.

Earliest reports on work-related homicide were largely anecdotal, relied on imprecise data, and lacked standardized definitions, case-ascertainment, or related methodologic factor. Few studies have examined differential risks by industries or occupational groups, and no studies have examined specific risk factors. Although general deterrence strategies are currently used to reduce employee risk, few counter measures designed for specific occupations have been scientifically studied or evaluated.

The problems in identifying work-related assault deaths are part of the overall difficulty of assessing risks for specific occupations and industries. The problem is multifaceted and includes two major obstacles, namely, the inability to use extant data sources to identify work-relatedness of the fatal injury and, second, the absence of a mechanism to simultaneously identify the occupation and industry of the worker who died. This inability to link health information from the death certificate with the corresponding police report results inprecise estimates of work-related homicides.

Objectives

The overall objective of the proposed research is to understand the magnitude and identify the determinants of work-related assault injuries. To accomplish this objective, two specific aims will be undertaken: (1) to estimate the average incidence rates of fatal and hospitalized nonfatal work-related assault injuries in four Southern California counties between July 1991 and June 1993; and (2) to identify individuals, occupational, and environmental predictors of fatal and hospitalized non-fatal work-related assault injuries in selected high-risk occupations in the same four Southern California counties.

Methodology

A mixed design strategy will be used for (1) incidence determination and rate estimation; and (2) a case-control study to identify risk factors for fatal and nonfatal assaultive injury, and to estimate their effects.

Significant Findings

None to date.

Evaluation of a Database for Occupational Injury Surveillance

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

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

Importance to Occupational Safety and Health

Severe occupational injury is among the ten categories of leading work-related diseases and injuries identified by NIOSH for in-depth study and prevention. The New Jersey State Department of Health evaluated the usefulness of its statewide hospital discharge database ("UB-82" database) for surveillance and epidemiologic study of five severe, non-fatal, occupational injuries. Accurate surveillance can provide baseline estimates of the statewide incidence of these five types of work-related injuries which required hospitalization. Epidemiologic data gathered by personal interviews in this study can help target high-risk industries, occupations, machinery, and work behaviors for future intervention activities to prevent these injuries.

Objectives

The objectives of this study were to:

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

Methodology

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

Significant Findings

The hospital discharge data were compared with data collected by telephone interview of discharged patients. A total of 1,575 unique hospital discharge records for the selected injuries included: finger amputation (1,041), thumb amputation (209), crush injury of the lower limb (208), toxic effects of heavy metals (69), and eye burns (48). Of 809 study subjects sent letters, 445 (55%) could be contacted, and 289 (36%) were interviewed for the study. Sixty-one percent (175) said their injury was work-related. A comparison was made between self-reported injury at work and the presence of workers' compensation payer codes on the discharge database. The agreement beyond chance (Kappa) was 0.78 (95% CI = 0.67,0.89). The sensitivity of this indicator of work-relatedness was 83%; specificity was 98%. These data suggest that workers' compensation payment on the hospital discharge database may be a good to excellent proxy indicator of the work-relatedness of these injuries. Limitations include the 17% underestimate of work-related injuries using the workers' compensation payer codes.

Further analysis of the finger amputation cases was done. A total of 637 persons hospitalized for finger amputations were sent letters asking for their participation. Of 637 persons, 355 (56%) were contacted and 228 (36%) were interviewed of whom 134 (59%) said their injury occurred at work. The annual rate of finger amputations at work was

9.3 per 100,000 employed persons. The rate was higher for males (14.7) than females (1.9). The age-adjusted rates were higher for Hispanic (52.8) and black (28.9) males than for white males (9.5). Persons working with machines, or maintaining them, in the manufacturing industry were at highest risk. Unjamming or repairing machinery (e.g., presses, saws or slicers) while in operation was particularly hazardous. These data can be used to target occupations and industries for specific worksite intervention to prevent finger amputations. One limitation of this analysis, however, is that hospitalized occupational finger amputations may not be representative of all finger amputations, the majority of which are less severe and do not require hospitalization.

The Effect of Localized Fatigue on Postural Stability

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

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Grant Number: *5 R03 OH02653-02*
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Funding Level: *$22,690 ($43,365 Cum)*

Importance to Occupational Safety and Health

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

Objectives

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

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

The specific objectives for year two of the project are:

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

Methodology

A total of 36 healthy males, aged 21-35 years, will be studied during each experiment. Males were chosen because of the stressful nature of the lifting task. Fatigue estimates of standing steadiness, heart rate, ratings of perceived exertion, and ratings of discomfort will be the dependent variables to be collected prior to and following each condition for all experiments. During Experiment One, subjects will be exposed to fatigue of six postural muscle

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

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

Significant Findings

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

Analysis of Seafood Processing Injuries/Illnesses

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

Program Area: *Traumatic Injuries*
Grant Number: *1 R03 OH02656-01*
Start & End Dates: *02/01/90 – 01/31/92*
Funding Level: *$19,159 ($19,159 Cum)*

Importance to Occupational Safety and Health

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

Objectives

The objectives of the study are:

1. Develop demographic and occupational profile of workers injured in the seafood processing industry in Alaska over the three year period 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. Seventy-five percent of all work-related injuries sustained by workers in the canned/cured and fresh/frozen arm of the seafood process industry occurs within the first months of employment.
2. The nature of the injuries by frequency involved sprains and strains (35%), contusions and bruises (17%), cuts and lacerations (12%) and fractures (8%).
3. The body parts most frequently involved in work-related injuries were wrists, hands and fingers (26%) and trunks/backs (30%).
4. Injuries clustered around two broad occupational groups: the pack/fillet machine operators (27%) and miscellaneous handlers/workers (48%).
5. Sprains and strains of the back were the most frequently reported injuries for both occupational groups (33%), followed by cuts and lacerations to the hands and fingers (16%), contusions to the hands and fingers (9%), and fractures to the hands and fingers (4%).
6. Nerve injury to the wrists and hands accounted for 1.5% of the work-related trauma among pack/fillet machine operators and 2.8% of the injuries among the miscellaneous handlers/workers. Wrist and hand nerve injury 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

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

Program Area: *Traumatic Injuries*
Grant Number: *7 R03 OH02659-03*
Start & End Dates: *06/01/89 - 03/31/92*
Funding Level: *$21,300 ($42,691 Cum)*

Importance to Occupational Safety and Health

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

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)

Stress Effects of Human-Computer Interactions

Henry H. Emurian, Ph.D.
The University of Maryland
Information Systems Development
Baltimore County Campus
Baltimore, Maryland 21228

Program Area: *Cardiovascular Diseases*
Grant Number: *1 R01 OH02614-01A1*
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Funding Level: *$26,630 ($26,630 Cum)*

Importance to Occupational Safety and Health

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

Objectives

This research aims to compare blood pressure and heart rate responses exhibited by Type A and Type B male and female volunteers, who are experienced computer users, during work on a data retrieval task undertaken at a video display terminal (VDT). Hasseter (jaw) electromyograph (EMG) responses will also be obtained as real-time "microaggressive" responses emitted by operators during human-computer interactions. It is hypothesized that angry Type A users, in comparison to Type B users, will show elevated cardiovascular and EMG responses when system response time delays, which occur between the entrance of a query command and the final display of data, are either unpredictable or brief.

Methodology

A repeated measures group design, with a between-subject component on personality, was adopted for the research. Additionally, three subjects were studied over several consecutive daily sessions during individual subject observations. Subjects performed a synthetic data retrieval task, emulating a hospital information management system. Payment was contingent on accurate and rapid query solutions. Concurrently, measures of blood pressure, heart rate, and masseter EMG were obtained. All subjects received a 1-hour resting baseline on a day not also including task performance. Task performance included 2 successive conditions of variable and constant system response times or fast and slow system responses times, counterbalanced across subjects. Scores on the Videotaped Structured Interview were median split to determine differential cardiovascular and EMG responses between the resulting groups.

Significant Findings

In the first study, 10 untyped normal males solved 50 database queries consecutively presented on a video display terminal (VDT). Each query required solution within 45 sec of its initial presentation to avoid a reduction in potential earnings. A solution required the correct selection of 3 successive hypertext indices hierarchically structured from the query to the data answer. Under a constant system response time (SRT) condition, each selection of a hypertext index was followed by an 8-sec delay before another database level, consisting of both indices and data, was presented. Under a variable SRT condition, SRTs varied between 1 and 30 sec, with a mean of 8 sec. Twenty-five successive queries were presented under each condition, and the order of conditions varied unsystematically across subjects. Systolic blood pressure, mean arterial blood pressure, and heart rate showed pronounced elevations during task performance, in comparison to a resting baseline. Diastolic blood pressure and masseter muscle electromyograph (EMG) response did not change reliably over baseline. Intersubject variability in EMG response was, however, related to heart-rate variability during task performance. No differential physiological effects of SRT conditions were observed. An eleventh novice subject's cardiovascular responses habituated over 5 successive performance sessions, but when new queries were introduced, heart rate magnitude increased, showing the reversibility of the effect under novel performance demands.

In the second study, 16 male and 16 female volunteers solved the database task under slow and fast SRT conditions. Under the slow condition, SRT duration was 10 sec, and under the fast condition, SRT duration was 1 sec. Each subject received the Videotaped Structured Interview prior to the experiment. The procedure was identical to the first study, with the SRTs changed to produce low and high density time-pressured work and with 40 queries programmed under each condition. Results showed that systolic blood pressure, heart rate, and masseter EMG responses were greater during work, in comparison to the resting baseline. Systolic blood pressure was higher during the fast SRT condition, in comparison to the slow SRT condition. The latter effect was also observed over several successive performance sessions by 2 individual subjects, one male and one female. Females showed reliably greater masseter EMG responses during the fast SRT condition, in comparison to the slow SRT condition. Systolic blood pressure was higher for subjects above the median score on the Videotaped Structured Interview, in comparison to subjects below the median.

Publications

Emurian HH: Physiological Responses during Data Retrieval: Comparison of Constant and Variable System Response Times. Computers in Human Behavior 7:291-310, 1991

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

Vascular Effects of Chelation In Lead Exposed Workers

Michael J. Kosnett, M.D.
University of California, San Francisco
Occupational Health Clinic
SFGH, Building 9, Room 109
San Francisco, California 94110

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Start & End Dates: *09/30/91 - 09/29/94*
Funding Level: *$54,000 ($54,000 Cum)*

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.

Objectives

The primary objective is to elucidate the mechanism of lead's vascular effects in human subjects. Using established protocols that measure the pressor response to infused norepinephrine, we will investigate whether a reduction in soft tissue lead burden by EDTA chelation can reduce the vascular responsiveness of subjects with occupational lead exposure. Targeting enrollment to specific subject populations will enable the impact of racial and exposure intensity factors to be explored.

Methodology

Asymptomatic black men with blood lead concentrations between 25 and 80 ug/dl, indicative of occupational lead exposure, will be recruited as subjects from industries, unions, and physicians within the large referral network of the University of California, San Francisco Occupational Medicine Program. Fourteen nonmedicated subjects with diastolic blood pressure between 85 and 105 mmHg on two consecutive screenings, indicative of borderline to moderate hypertension, will be admitted to the UCSF General Clinical Research Center and stabilized for 48 hours on a fixed sodium diet. In each of 2 intervention cycles,

subjects will receive a stepped-dose infusion of norepinephrine (NE) (known to generate a linear blood pressure response), immediately before and after an experimental intervention, and the slope of the dose-response lines will be calculated. In one cycle, the intervention will consist of a 48-hour lead chelation with i.v. EDTA, in the other matched i.v. placebo. The order of the two cycles will be 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, will be compared between the chelation and placebo cycles. In a secondary analysis, linear regression will relate the change in slope to the change in blood lead concentration. To explore the specificity or generalizability of the results, the model will be subsequently applied to the study of (1) non-black subjects, (2) subjects with lower blood lead concentrations (eg less than 25 ug/dl), or (3) subjects in which positive trends are found.

Significant Findings

None to date.

Occupational Risks of Pesticide Exposure for Females

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

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Importance to Occupational Safety and Health

The emergence of females into the everyday workplace has catapulted attention of researchers to evaluate the exposure risk of toxic agents on the female reproductive system. That increased exposure risk to the human female in industry will escalate. It is readily apparent when one considers the recent Supreme Court ruling stipulating that women can no longer be discriminated against when applying for a position in which exposure to a hazardous agent is a reality. Female workers can no longer be prevented from being placed in such a position even though they are in their child-bearing years, and even though they may be pregnant and, as yet, unaware of it. The Court has ruled that the decision to work in such an environment is up to the woman herself. This situation demands that we evaluate not only exposure during pregnancy, but also exposure of females to toxic agents prior to pregnancy.

Objectives

This study is designed to evaluate the reproductive toxicity of the pesticide methoxychlor on both non-pregnant and pregnant female and the female offspring of the exposed mother. Several biological markers are being employed in this study. These markers include tabulation of different follicle populations in order to detect differential follicular sensitivity to the pesticide, histochemical evaluation of metabolically active enzymes within the ovary, and the use of lectin probes to detect ovarian cell membrane composition. It is anticipated that critical implementation 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 virgin female CD-1 mice were used in both phases of the experiment. Adult non-pregnant mice (7-10 weeks old) were exposed via oral gavage to specific doses of methoxychlor, estradiol-17β, or sesame oil. After four weeks of exposure, the ovaries were removed and prepared for light and electron microscopical examination for tabulation of the follicle populations. In the experiments involving exposure of pregnant females, mice were exposed daily to the pesticide from Day 6 to Day 15 of gestation. Offspring were evaluated at parturition as to their number, sex, weight, and any visible external malformations. Female offspring ($F1_a$) were cross-fostered among the differently treated mothers and times of vaginal opening recorded. In addition, mothers exposed to the pesticide during their first pregnancy were allowed to mate again following weaning, and their second set of offspring ($F1_b$) was similarly evaluated to detect any residual effects remaining following the initial exposure.

Significant Findings

Non-Pregnant Females

There was no growth retardation in mice exposed to methoxychlor for either two or four weeks. There was a dose-related response to methoxychlor with respect to the onset of persistent vaginal estrus (PVE). Animals exposed to 2.5 and 5.0 mg methoxychlor exhibited PVE in less than six days. Interestingly enough, animals exposed to estradiol took a mean of a little more than seven days to acquire PVE. The group receiving 1.25 mg methoxychlor took slightly longer than the estradiol group to reach PVE.

Ovarian weights did not differ significantly among the groups following two weeks exposure to methoxychlor. However, four weeks of pesticide exposure was enough to significantly decrease ovarian weight in the two higher methoxychlor-treated groups. Data acquired from tabulating the condition of large follicles (grater than 300μ) following two weeks of exposure to methoxychlor revealed no significant changes in the percentage of large follicles that were atretic. Following four weeks of exposure to methoxychlor, there was a significant increase in the percentage of large follicles that were atretic in mice treated with 2.5 and 5.0 mg methoxychlor when compared to that of controls. Similarly, the estradiol-17β group also exhibited a significant increase in the percentage of atresia in large follicles.

Electron microscopical studies on ovaries from animals exposed to 5.0 mg methoxychlor for four

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

Pregnant Females

Mice were exposed via oral gavage to 7.5, 5.0, or 2.5 mg methoxychlor or 0.025 mg estradiol-17β from Days 6-15 of pregnancy. Following delivery, female offspring (F_{1a}) were cross-fostered and sacrificed at 8 weeks of age. Mothers exposed during their first pregnancy were allowed to mate again and their second set of offspring (F_{1b}) were similarly evaluated to detect any latent effects from the initial exposure. Mice exposed to 7.5 mg methoxychlor were unable to carry their litters to term. Results revealed a significant increase in the length of gestation of mice exposed to both E-17β and 5.0 mg methoxychlor. A larger percentage of atretic follicles appeared in the ovaries of F_{1a} females which were exposed prenatally to 5.0 mg methoxychlor when compared to controls. Females from the F_{1b} litter displayed a significant advance in time of vaginal opening. This demonstrates that a subsequent litter of a mother exposed during a previous pregnancy to methoxychlor can also be affected. It is, therefore, imperative when performing any toxicological study on pregnant animals, to allow the mother exposed during the first pregnancy, to mate again and then evaluate any latent effects on the subsequent litter (F_{1b}).

Publications

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Adverse Reproductive Events and Electromagnetic Radiation

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

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Importance to Occupational Safety and Health

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

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

Objectives

To determine the risk of reproductive loss and major/minor anomalies among PTs and their offspring, female PTs have been surveyed by mail. The reproductive experience of women, and in particular, fetal loss, will be compared to the reproductive experience of women with little or no EMR exposure. Both long-term and short-term exposure to EMR prior to and during pregnancies are being considered.

Methodology

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

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

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

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

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

Significant Findings

Female physical therapists who work with microwave diathermy are at increased risk of experiencing a recognized early fetal loss, but female physical therapists who work with shortwave diathermy are not at an increased risk. This association holds even when mother's age at conception, the number of years elapsed between conception and the interview, the number of prior early fetal losses, mother's conditions ever diagnosed, and use of other modalities are controlled.

Occupational Exposures and Birth Defects

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

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

Methodology

We will develop methods whereby occupational exposures identified by the JEM can be applied to the existing BDS data base in order to develop joint distributions of specific occupational exposures and specific birth defects; these distributions will then be used as a resource for testing and generating hypotheses concerning occupation and birth defects. This research effort consists of three phases. In the first phase, we have 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 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 enables us to assess both the representativeness of this data base and to reflect 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 will serve as the primary tool for subsequent testing and generation

of hypotheses regarding occupational exposures and birth defects.

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

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

Significant Findings

None to date.

Menstrual Function and Physical and Mental Job Stress

Maureen C. Hatch, Ph.D.
Columbia University
School of Public Health
Division of Medicine
600 West 168th Street
New York, New York 10032

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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 menstrual 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, E_1G 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 (<10th percentile); highly variable (change in length >7 days); 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 sampling for cortisol, one of the stress hormones, may be carried out on at least some of the study subjects. Stress-related behaviors like caffeine consumption and exposure to antineoplastic medications will also be studied. 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. To examine the validity, using urine hormone data as the gold standard, of two less demanding tools for measuring menstrual

function in future field studies -- basal body temperature records and menstrual diaries.

Methodology

We propose to enroll 100 female nurses, 50 each drawn from high and low stress areas of Memorial Sloan-Kettering Cancer Center (MSKCC), for three consecutive menstrual cycles. Subjects will be 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 will be analyzed for estrone-3-glucuronide (E_1G), pregnanediol-3-glucuronide (PdG), luteinizing hormone (LH) and creatinine (CR). Nurses were selected as the target population because of high job stress levels, and because high caffeine intake and willingness to comply with a demanding regimen also seemed likely; a feasibility study conducted at MSKCC supports this. High and low stress units at MSKCC are identified on the basis of archival material and discussions with administrators.

Data analysis will evaluate the relations in the intensity of job-related stressors, caffeine consumption, and exposure to antineoplastics, and several measures of menstrual function (cycle length: ovulation; and luteal phase adequacy). Absolute levels and rates of E_1G and PdG will also be compared in relation to exposure. Finally, to aid in the design of future menstrual studies, the validity of basal body temperature and prospectively ascertained reports of menstrual cycles will be assessed, using the urinary hormone data as a gold standard.

Significant Findings

None to date.

Adverse Pregnancy Outcomes Among Cosmetologists

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

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Importance to Occupational Safety and Health

Cosmetology, a predominantly female employment sector, entails two potential hazards to reproduction: chemical exposures and physical work demands such as prolonged standing. Cosmetologists are in daily contact with a wide range of cosmetic products such as shampoos, rinses, hair dyes, permanent wave solutions, hair straighteners, hair sprays, make-up, perfumes, nail polish, polish remover, artificial nails, detergents, antiseptics, and sterilizing solutions. Through inhalation and dermal absorption cosmetologists are therefore routinely exposed to multiple chemical substances.

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

Objectives

The objective of this study was to assess whether female employment in cosmetology during pregnancy increases the risk of spontaneous abortion prior to 20 weeks gestational age, pre-term delivery, and low birthweight, and whether the risk of adverse pregnancy outcomes varies by type and intensity of chemical exposure.

Methodology

A mail survey was conducted in 1988 among licensed cosmetologists in North Carolina in order to identify women with a pregnancy conceived during a five-year period from 1983 to 1988. We sent a two-page screening questionnaire to 8,356 female cosmetologists, aged 22-36 years in 1988, inquiring about demographic background, recent health problems, reproductive history, outcome of the most recent pregnancy, and work status during the most recent pregnancy. With a 74% response rate, 1,429 single live births and 145 spontaneous abortions of less than 20 weeks gestational age were reported among the most recent pregnancies conceived between 1983 and 1988. An additional 122 spontaneous abortions were identified among previous pregnancies conceived from 1983 to 1988.

Cosmetologists with an eligible pregnancy were sent a second questionnaire which requested more detailed information on the outcome of the index pregnancy, work exposures during pregnancy, and other potential risk factors for adverse pregnancy outcomes. Chemical exposure in cosmetology was not directly measured, but assessed by self-reported work activities and salon characteristics for the job held during the index pregnancy (e.g., number of hours worked per week; weekly number of customers, hair dyes, bleaches, permanents; use of formaldehyde; wearing of gloves; number of cosmetologists working in salon; performance of manicuring or nail sculpturing by other employees).

The response to the detailed questionnaire was 74%, yielding data on 191 spontaneous abortions and 1,058 single live births. The first set of analyses assessed the risk of spontaneous abortion among cosmetologists. Mothers with a spontaneous abortion were compared to those with a single live birth with regard to their work performed during the first trimester of pregnancy. All subjects were licensed cosmetologists, with "exposure" defined as working in cosmetology during the first trimester of pregnancy. The unexposed referent group included licensed cosmetologists who worked in other jobs during the first trimester of pregnancy. Logistic regression modeling was conducted and adjusted odds ratios (aOR) and 95% confidence intervals (CI) were computed, controlling for previous pregnancy loss, gravidity, maternal age at conception, family income, maternal alcohol consumption and cigarette smoking during the first trimester, and number of hours worked per week.

Significant Findings

Compared to the unexposed referent group of women who worked full-time (35 or more hours per week) in other jobs during the first trimester of pregnancy, elevated odds ratios were associated with full-time (35 or more hours per week) work in cosmetology (aOR = 1.3, 95% CI = 0.8-2.3) and attendance of cosmetology school (aOR = 2.6, 95% CI = 1.2-6.0). Part-time work in cosmetology (aOR = 1.0) and full-time work as a homemaker (aOR = 1.1) were not associated with an increased risk of spontaneous abortion. For full-time cosmetologists categorized by several measures of chemical exposure, the adjusted odds ratios for the highest exposure levels were 1.7 (95% CI = 0.8-4.0) for 60 or more customers per week, 1.5 (95% CI = 0.6-3.7) for 3 or more bleaches, 1.5 (95% CI = 0.8-2.7) for 3 or more dyes, and 1.8 (95% CI = 0.9-3.6) for 10 or more permanents. Positive associations were also found for the use of formaldehyde to sanitize equipment (aOR = 1.9, 95% CI = 1.0-3.1), and working in salons where manicuring (aOR = 1.5, 95% CI = 0.8-2.9) or nail sculpturing (aOR = 1.9, 95% CI = 1.0-3.8) were performed by other employees. Personal use of hair dyes and permanents during the first trimester of pregnancy was not associated with increased spontaneous abortion risk.

Despite incomplete response and limitations of self-reported exposure and disease information, these data suggest that full-time work in cosmetology may be associated with an increased risk of spontaneous abortion. The results warrant further research into reproductive hazards in cosmetology.

Publications

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Occupational Neuropathies Due to Industrial Chemicals

Mohamed B. Abou-Donia, Ph.D.
Duke University Medical Center
School of Medicine
Department of Pharmacology
Box 3813
Durham, North Carolina 27710

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Importance to Occupational Safety and Health

Exposure of humans to one or multiple neurotoxic chemicals results in neuropathies. The major goal of this project is to develop methods for screening or monitoring workers for over-exposure to neurotoxicants. This goal will be accomplished by improving our understanding of basic mechanisms of neurologic disorders following exposure to one or multiple chemicals. Aliphatic hexacarbons, i.e., n-hexane and MnBK are used in the textile industry while organophosphorus compounds are used in pesticides and industry. National Occupational Exposure Survey, in 1980-1982, estimated the number of workers exposed to n-hexane to be 838,554. Worldwide, approximately 2.1 million persons are exposed to n-hexane. Organophosphorus compounds produced in the U.S. in 1981 were more than 396.5 million pounds.

Objectives

The overall objective of this project is the prevention of chemically-induced neurodegenerative disorders upon occupational exposure to neurotoxicants. We plan to develop biomarkers for early detection of exposure to aliphatic hexacarbons and organophosphorus compounds by studying the target proteins in the nervous system. Also, we will ascertain the development of neuropathy associated with the single, simultaneous, and sequential exposure to these chimeras.

Methodology

For the first specific aim, we plan to investigate the use of antibodies to specific neurotoxic chemicals for the development as biomarkers for the early detection of exposure to industrial chemicals. The antibodies will be chemical specific, i.e., 2,5-hexanedione and triphenyl phosphite, that will recognize protein bound neurotoxicant regardless of bound protein. To accomplish this aim, we will first prepare modified antigens to mimic an *in vivo* response to the neurotoxicant. Since both aliphatic hexacarbons and organophosphorus compounds are known to irreversibly bind to proteins, we should be able to successfully generate haptens. By doing so, we will then be able to generate both polyclonal and monoclonal antibodies to the specific hapten epitope. In each case polyclonal formation will be assayed to study (1) the feasibility of obtaining epitopic specificity and (2) to ascertain that the polyclonal antibodies react preferentially to the hapten conjugated protein and not to the native carrier protein. Monoclonal antibodies could then be developed to enhance the sensitivity and specificity of the tests.

For the second specific aim, we will examine if any synergistic effects occur, rats will also be exposed concurrently to aliphatic hexacarbons and organophosphorus compounds by exposure to n-hexane and triphenyl phosphite by inhalation and dermal application, respectively.

Significant Findings

To date, we have successfully prepared a protein hapten conjugate as well as generating monoclonal antibodies to the hapten. The hapten was synthesized by forming a 2,5-hexanedione derivative of bovine serum albumin. By Coomassie blue and silver staining of SDS PAGE gels, a single protein band which migrated slightly more rapidly than native BSA could be detected. We plan to fully characterize this hapten by amino acid analysis and mass spectrometry. Monoclonal antibodies were produced. Elisa analysis of the polyclonal sera of immunized mice indicated a specificity for the modified protein BSA indicating that the antibodies were directed toward the hapten. The mice were then used to generate several monoclonal antibodies. The monoclonals will be used to analyze nervous tissue and plasma of 2,5-hexanedione-treated rats for the presence of antigen, i.e. adducts to protein. Preliminary results on spinal cord isolated from 2,5-hexanedione-treated rats showed a specific interaction of antibody to neurofilaments as demonstrated by both a dose-response curve to antibody and increase of reactivity over control samples. To mimic occupational exposure, rats will be subjected to n-hexane (which is metabolized *in vivo* to

2,5-hexanedione) by inhalation. A complete time course will be carried out to determine the earliest time point in which an immune response can be detected to the neurotoxicant. This will be accomplished by monitoring plasma samples over time for their presentation of antigen, i.e., hapten.

Publications

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Peripheral Markers of Styrene Toxicity

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

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Importance to Occupational Safety and Health

Adverse effects from occupational chemical toxicants typically are only detected when related health outcomes are severe following periods of intense exposure. Morbidity and mortality are the usual indicators of toxicity. Effects to the nervous system increasingly are being recognized as important endpoints for epidemiologic and clinical research in the workplace. There is also a growing trend in occupational health research to develop and validate methods for early detection of biochemical changes caused by toxic workplace exposures. The goals of this approach are to assess potential risks to health before overt morbidity occurs and to reduce or eliminate hazardous agents from the workplace. Biological monitoring is the term often used in this context. Biological monitoring can consist of measurement of toxicants, determination of biological response to toxic exposures, or determination of genetically-determined host factors that render persons more or less susceptible to toxicity. This project involves the application of exposure and biological response biomonitoring among workers exposed to the industrial neurotoxicant, styrene. Peripheral blood and urine are used as the media for exposure biomonitoring, and peripheral blood cells are assayed for response to styrene. If the biomonitoring methods developed in studies such as the present investigation prove to be applicable for epidemiologic research, then this strategy will be a valuable approach for detection and prevention of chemical-induced toxicity.

Objectives

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

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

Methodology

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

Two surveys were conducted, the first in May, 1989, and the second in October, 1989. At the first survey, a questionnaire was administered eliciting data on demographics, work history, alcohol use, smoking, and medical history, including recent nervous system symptoms. At both surveys, 8-hour time weighted average breathing zone air concentrations of styrene were measured by personal monitoring using passive diffusion badges. Also, blood samples were obtained for styrene

concentration measurements, and urine samples were assayed for styrene metabolites, and mandelic and phenylglyoxylic acids. Sigma receptor binding was assayed against three ligands: 3-H-Spiperone, Haloperidol and di-toluyl-guanidine (DTG). MAO-B activity and 5HT uptake in platelets were assayed using standard techniques. GST and EH activities in lymphocytes were determined using benzo(a)pyrene as the substrate.

Significant Findings

Comparative analyses of styrene air concentrations, urine metabolites, and blood styrene concentrations revealed high degrees of correlation at both surveys (r-values ranging from 0.6-0.9). This suggests that biological monitoring at convenient times (i.e., mid-shift) can provide meaningful results. Blood styrene levels were used as the primary exposure indicator in the analyses of the symptom and biomarker data. Increasing trends of prevalence with increasing blood styrene levels were detected for the following CNS symptoms: headaches, dizziness, light-headedness, fatigue, irritability, memory loss, and feeling "drunk" at work, as well as for numbness or tingling in the hands and feet. These findings are consistent with previous literature. With respect to the biomarker data, no consistent trends were noted for sigma receptor binding, GST, or EH. MAO-B was inversely correlated with blood styrene level, whereas a slightly positive correlation was noted for serotonin uptake. A provocative finding was the relationship between MAO-B and prevalence of CNS symptoms. From the first survey, mean values of MAO-B (adjusted for age, gender, race, alcohol use, smoking, and employment duration) were 26.4, 46.4, 16.9, and 5.5, respectively, for subjects reporting 0, 1, 2, and 3 or more CNS symptoms. Symptom prevalence was not determined at Survey 2; thus, this association could not be evaluated. Liver transaminases did not appear to be affected by exposure level.

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Neurologic Effects of Solvents and Age in Older Adults

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

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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

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

Program Area: *Neurotoxic Disorders*
Grant Number: *5 R01 OH02719-02*
Start & End Dates: *02/01/90 – 01/31/92*
Funding Level: *$180,227 ($413,327 Cum)*

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 proposed OSHA PEL of 25 ppm.

Objectives

Based on a pilot study, a frontal/limbic system behavioral hypothesis is offered as the site of underlying pathology for subclinical PCE effects. The behavioral hypothesis posits that functions such as the ability to alternate between tasks and other tests requiring integration of complex attention and viscuo-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. Alternatively, potential deficits could be related to hippocampus and brain stem activity assessed separately by neurophysiologic electroencephalograms and visual evoked potentials.

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. An additional group of retired dry-cleaner operators (n=20) is also being tested.

To control for acute exposure effects, the symptom and behavioral evaluation 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 includes the following tests:

Function	Mode	Test	Method
Motor:	MD	One Hole	C
Attention:	VS	NES Digit Span	C
	VB	Oral Digit Span	P
Cognitive	VS	Trial Making	P
Flexibility:	VB	PASAT	P
Reasoning:	VS	Similarities	P
	VB	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
M = Math
MD = Manual Dexterity
P = Paper
VB = Verbal
VC = Vocabulary
VS = Visual

A pre- and post-exposure alveolar breath sample is measured to control for variation in PCE body burden, supplementing 8-hour air monitoring for each exposed and one out of every eight non-exposed workers. Exposure zones will be based on (1) distance from PCE source, (2) PCE air levels, and (3) PCE breath levels. Full-shift continuous PCE peak sampling (Bruel and Kjaer 1302) is being conducted on operators with fluctuating exposures. These exposure measures are used to construct lifetime indices of cumulative exposure. The 2-hour neurophysiologic assessment occurs at least 24 hours post-exposure on a separate day. Paid volunteers must have at least 1 year on the job, be older than 18-years old, English speaking, and have 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 shop, volunteers from each exposure zone will be tested. Potential confounding effects of age and education will be controlled by measures of stratification and multiple regression.

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

Significant Findings

Data collection is still 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.

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Validity of Computerized Tests in Occupational Settings

Roberta F. White, Ph.D.
Boston University Medical School
Department of Neurology
720 Harrison Avenue, Suite 801A
Boston, Massachusetts 02118

Program Area: *Neurotoxic Disorders*
Grant Number: *1 R01 OH02767-01A1*
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Funding Level: *$198,184 ($198,184 Cum)*

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.

The Effects of Impulse Noise on the Auditory System

Donald Henderson, Ph.D.
Research Foundation of SUNY
School of Social Sciences
Communicative Disorders and Sciences
215 Parker Hall
Buffalo, New York 14214

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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 "priming" exposures to non-traumatic noise can reduce the amount of hearing loss from a dangerous noise exposure.

Methodology

Several mechanical or electrical-mechanical devices are used to produce realistic noise impacts. Hearing is tested, the animal is exposed to impulse/impact noise, and its hearing is tested 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

William W. Clark, Ph.D.
Central Institute for the Deaf
818 South Euclid
St. Louis, Missouri 63110

Program Area: *Noise-Induced Hearing Loss*
Grant Number: *5 R01 OH02128-07*
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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. Careful evaluation of the ANSI- S12.13 database provided by NIOSH has revealed that U.S. workers exposed to noise below 85 dBA TWA 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). In replotting the Annex B data from original sources, three errors in the Annex have been identified.
8. Measures of noise exposure made in proximity to a hand-held walkie talkie are inflated by electromagnetic interference with the dosimeter, and can result in measured doses which exceed actual noise exposure by as much as 30 dB. Some interference was observed in 5 brands of dosimeters tested under laboratory conditions. Users are cautioned against operating radio transceivers in near proximity to the microphone cable of the dosimeter.

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Hearing Hazard Associated with Industrial Noise Exposure

Roger P. Hamernik, Ph.D.
Research Foundation of SUNY
107 Beaumont Hall
Plattsburgh, New York 12901

Program Area: *Noise-Induced Hearing Loss*
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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. Analytical methods using adaptive noise cancellation are being developed to decompose the complex noise into Gaussian and

non-Gaussian components, and complex cepstral analysis and frequency domain kurtosis procedures are being explored as methods for extracting quantitative information from the complex noise. The animal experiments being conducted use a standard paradigm. Chinchilla are being exposed for five continuous days to various complex noises. Hearing thresholds are obtained prior to exposure and at regular intervals following exposure using brain stem evoked potentials. Sensory cell populations are obtained from each animal, and relations between noise parameters, audiometry, and histology are derived.

Significant Findings

1. A digital noise generation system which relies upon manipulations of the phase spectrum can be successfully used to produce noise exposure stimuli of constant energy, fixed spectrum, and a variable kurtosis. The system which is designed to generate non-Gaussian signals in "real time" can effectively simulate a wide variety of complex industrial noise environments.
2. 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. For each of the two levels studied, the non-Gaussian exposures produced the greater loss. Another interesting feature of these results was that 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 2 to 4 kHz diverged so that there was up to 20 dB greater PTS than in the Gaussian exposures at high frequencies (to 16 kHz). 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 post-mortem 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.
3. On the basis of our earlier results, as well as those summarized above, new methods for the analysis of complex industrial noise environments need to be developed in order to evaluate complex noise environments for their potential to cause hearing loss.

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Prediction of NIPTS, Hearing Impairment and Handicap

Karl D. Kryter, Ph.D.
San Diego State University
Department of Communicative Disorders
5300 Campanile Drive
San Diego, California 92182

Program Area: *Noise-Induced Hearing Loss*
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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. There are differences of about 10 dB between the hearing levels of the so-called control groups (including those screened for exposure to noise and nosocusis) employed in most NIPTS studies, and those to be expected for persons screened for exposure to noise and nosocusis, according to ISO Standard 1999. The "control" groups have the worst hearing. This poor hearing on the part of the control groups prevents, of course, the detection of hearing loss from low-level noise exposures. Critical examination of specific study protocols, and recently developed information regarding contributions of nosocusis and exposures to gun noise to hearing loss in industrial workers, will be used during the project in an attempt to reconcile NIPTS data that appear to be confounded by the effects of these two factors.

Correspondence with Douglas Robinson regarding an important issue about his study of, and method for, predicting NIPTS has not as yet resolved this matter. The issue concerns a possible error in his analysis leading to an underestimation of NIPTS. The Robinson methodology served as a basis for ISO Standard 1999, and is of great significance to this field of research. Dr. Robinson has informed me he will shortly reexamine his data files to settle the question we have raised.

Objective 2. Correlation and multiple regression coefficients among all the variables taken, and created, from the U.S. Public Health survey have been completed. Preliminary inspection of the results show interesting and statistically significant relations among the variables. Interpretation of these statistics remains to be done.

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I.D. and Evaluation of Noise in Vocational Education Laboratories

Glen M. Miller, Ed.D.
The University of Arizona
College of Agriculture
Department of Agricultural Education
Forbes 226
Tucson, Arizona 85721

Program Area: *Noise-Induced Hearing Loss*
Grant Number: *5 R03 OH02671-02*
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Importance to Occupational Safety and Health

Vocational education laboratories in programs such as Trade & Industrial Education, Industrial Arts Education, and Agricultural Education, are equipped with tools and machinery which duplicate those used in the industry for which students are preparing.

The majority of vocational educators do not recognize the risk which noise poses to their students or themselves. Teachers lack basic information about the exposure levels they and their students experience in their instructional laboratories.

Objectives

1. To survey and develop an inventory of the power tools and equipment found in selected vocational education laboratories in Maricopa and Pima Counties, Arizona.
2. To measure the noise level in dB(A) of common power tools and equipment used in selected vocational education laboratories in Maricopa and Pima Counties, Arizona.
3. To document the acoustical characteristics of the selected facilities which could have impact on noise levels.
4. To measure student and teacher percent dose in each facilities environment.
5. To disseminate findings and recommendations to vocational educators and administrators of vocational education programs by all available means, including periodicals, journals, and direct mailing to teachers.

Methodology

This study was conducted as descriptive research with survey data collected on site by researchers. The accessible population included all students enrolled and teachers of programs in the areas of Trade and Industrial Education, Industrial Arts Education, and Agricultural Education at the secondary level in the state of Arizona. Approximately 38,547 students were enrolled in these programs in 1987 in Arizona.

The target population included secondary school students enrolled in agricultural education, trade & industrial education, and industrial arts programs in Pima and Maricopa Counties where welding is specified as a part of the curriculum or the major emphasis of the course. Pima and Maricopa Counties contain 75% of the population of the state of Arizona.

Significant Findings

Noise Levels of Common Power Tools - The sound pressure level readings on the inventoried power tools were conducted using uniform materials provided by the researcher. The levels were very high for some tools. The average reading over all shops for abrasive cut off saw was 101.7 dB, 100.5 for the portable grinder, 102.5 for the power circular saw, 101.2 for the radial arm saw, 106.7 for the air chipping hammer, and 106.5 for the electric impact wrench. These sound levels are especially significant for the vocational education teacher who may be exposed over five or more class periods per day.

Acoustical Characteristics of Vocational Education Laboratories - Measurements were made of the reverberation time for each laboratory. One laboratory had a RT60 value of .6 seconds, 6 had a value of .8, 3 had a value of 1.0, and 3 had a value of 1.2 seconds. A second grouping had a RT60 value of 1.6 (2), 1.8 (1) and 2.0 (2) seconds. The longest reverberation times were recorded in 3 programs with values measured of 2.4 seconds, 2.6 seconds, and 2.8 seconds respectively.

Student and Teacher Noise Dose - Student and teacher doses are significant based upon the measurements taken. Of the 104 students and teachers measured, 73 would meet or exceed the OSHA recommended dose if the same exposure measured were continued over an 8 hour period. This fact, when combined with other potential environmental noise in this age group, gives rise for concern. Single noise events using a 3dB exchange rate were also high. All participants experienced levels above 112 dB with one experiencing a weighted single event of 132 dB. On an unweighted scale, one student experienced a noise level of 144 dB. There were a total of 6 instances where a student or teacher exceeded 140 dB.

Student and teacher dose were not correlated to the acoustical characteristics of the facilities. This failure to find correlation was a function of the difference between the acoustical environment of the welding booth compared to the shop. In almost all cases, the welding booth had little if any acoustical treatment and was in effect an independent environment from the shop.

Conclusions - Vocational education laboratories in Pima and Maricopa Counties, Arizona are equipped with tools and equipment that develop high levels of noise. These tools and equipment are in various states of repair with a significant number in unsafe operating condition. Less than half of the school shops had any acoustical treatment. The lack of acoustical treatment led to noise reverberating for long periods of time in nearly half of the shops. Some students and teachers are routinely receiving potentially damaging noise doses while welding in vocational education laboratories. The magnitude of this damage cannot be estimated due to a lack of knowledge of the exposure of students and teachers to noise outside of the shop environment. It is clear that if the welding activity measured was continued for 8 hours, 70 percent of the students and teachers would exceed OSHA recommended levels of exposure.

Publications

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Symposium: Noise-Induced Hearing Loss

Donald Henderson, Ph.D.
State University of New York at Buffalo
Parker Hall, Room 105
Buffalo, New York 14260

Program Area: *Noise-Induced Hearing Loss*
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Importance to Occupational Safety and Health

The proposed conference was designed to integrate the current state of knowledge on the biological bases and applied aspects of noise-induced hearing loss. In the past five years, scientists have made considerable progress in understanding the active processes in the cochlea and the cell biology and biochemistry of hair cells. Advances have also been made in understanding the parametric relation between acoustic variables and hearing loss and how the effects of noise can be influenced by other non-acoustic variables (particularly impulse/impact noise). In addition, engineers have developed devices that more accurately capture the "noise dose" under a wide range of exposure conditions. Progress has also been made in the design of hearing protection devices. For society to use the new information and for scientists to continue to make progress, it is important to provide a forum to integrate results across disciplines and provide insights for future research. The proposed conference brought together experts from most of the disciplines interested in noise-induced hearing loss. Each participant presented a critical review of a topic along with their most recent findings. To disseminate this information to an even broader audience, the papers and discussions will be edited and published.

Immunotoxicology of Phenols on Epidermal Immune Cells

James J. Nordlund, M.D.
University of Cincinnati
College of Medicine
Department of Dermatology
231 Bethesda Avenue, ML #592
Cincinnati, Ohio 54267-0592

Program Area: *Dermatological Conditions*
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Importance to Occupational Safety and Health

Cutaneous disorders are one of the most common occupationally related problems. Although they rarely cause death, they are responsible for significant morbidity, i.e., loss of time from work, discomfort, and secondary infections. Most occupational skin disorders are considered a form of contact dermatitis. Contact dermatitis is subclassified into two categories, allergic (immunologically mediated) and irritant. Numerous epidemics and individual episodes of occupationally related skin disorders have been carefully evaluated to determine the offending chemical(s) and the pathogenesis (immune or irritant mediated). Occasionally these investigations are successful. More commonly, no specific chemical(s) can be identified as the inciting agent(s).

Since the 1930's it has been well documented that antioxidants like monobenzone or paratèrt butylcatechol cause leukoderma, i.e., a loss of melanocytes from the epidermis. Not all subjects, however, exposed to these agents, even in very high concentrations such as 40% creams for periods of up to two years, develop leukoderma. This suggests two conclusions: (1) that individuals have different susceptibility to the injurious effects of antioxidants; and (2) that these compounds are not simple toxins for pigment cells.

Antioxidants like butylated hydroxytoluene and monomethyl ether of hydroquinone (4-hydroxyanisole) are ubiquitous chemicals, similar in their structure to the known leukodermic agents. They are present in virtually all foods, medicinal creams, and many occupational and daily settings. We have studied the effects of monobenzone, paratert butylcatechol, butylated hydroxytoluene, and monomethyl ether of hydroquinone applied to skin of mice. We found that these agents can alter the number of cells expressing class II antigens. Some of the animals exhibit *in vivo* hyperreactivity to subsequent exposure to known allergens like DNCB. These compounds also increase the expression of Thy-1+ molecules and the number of Thy-1+ dendritic epidermal cells, a group of lymphocytes which are thought to be T-suppressor cells. However, the immune responsiveness of animals with increased amounts of Thy-1 cells to subsequent exposure to known allergens is not simply dependent on the morphologic changes nor simply on the ratio or quantity of Ia (activator) to Thy-1+ (suppressor) cells. Results of both *in vivo* and *in vitro* studies show that the immune/inflammatory responsiveness of epidermal cells of animals exposed to antioxidants is altered but in an intricate and complex manner. We conclude that antioxidants which are ubiquitous in our daily lives are not biologically inert, but rather alter the function of the skin in subtle ways. Subsequent exposure to other chemicals and environmental agents like sunlight produces inflammatory responses different from those that would be observed in skin not predisposed by exposure to these chemicals. We propose that some of the mysteries of some occupationally-related cutaneous problems will be resolved by studying the effects *in vitro* and *in vivo* of these common antioxidants on epidermal cells.

Objectives

Our major hypothesis is that antioxidants are not inert, but rather alter the inflammatory/immune responsiveness of the skin. Two cytokines produced by various cells of the skin are thought to be initiator signals for inflammation, specifically interferon-γ (IFN-γ) and IL-1. A third cytokine, α-MSH, seems to be a potent and natural antagonist (suppressor) of some interferon and IL-1 mediated activities. A fourth cytokine is a traffic signal, the intercellular adhesion molecule (ICAM), and it is needed to attract and retain inflammatory cells within the epidermis. We suggest that these four molecules compose at least part of a self-regulating immune/inflammatory system within the skin. We propose to study the effects of antioxidants on the initiator, suppressor, and trafficking molecules.

Methodology

We are using two strains of mice, the C57BL/6 and its congenic mutant C57BL/Ler-vit/vit mouse. The latter mouse exhibits all the features of an animal highly susceptive to antioxidants. It exhibits

leukoderma and altered epidermal immune reactivity. We are studying the effects of antioxidants on the function of Langerhans cells, lymphocytes, melanocytes, and keratinocytes *in vitro* and *in vivo* from these animals on the expression of the initiator suppressor signals. We are using immunofluorescence, immunoelectron microscopy, molecular probes, as well as *in vitro* functional assays such as mixed epidermal lymphocyte reactions.

Significant Findings

We have documented with a high degree of probability that α-MSH is synthesized within the epidermis. The source at least of MSH seems to be either the melanocyte and/or Thy-1 lymphocyte. In addition, melanotropic agents and melanocytes seem to be essential components of the immune/inflammatory regulatory loop. Loss of melanocytes is accompanied by loss of inflammatory responsiveness. α-MSH is a potent melanotropic stimulant and an immune suppressant. α-MSH blocks both the afferent and efferent cutaneous immune responsiveness which can be reversed by simultaneous administration of interleukin-1. It should be noted that antioxidants markedly increase the production of IL-1 *in vitro* and probably MSH expression as well. The effects of antioxidants on interferon-γ and ICAM are under study.

We have also documented that IL-1, IL-6, TNF-α, and IFN-γ all alter melanocyte function. Our final goal is to understand how these four biological modifier molecules interact and how that is altered by ubiquitous antioxidants. We will use the information for these studies in an attempt to understand better occupationally-related skin disease.

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Biological Monitoring for Exposure to Coal Tar

Regina M. Santella, Ph.D.
Columbia University
Division of Environmental Science
650 West 168th Street
New York, New York 10032

Program Area: *Dermatological Conditions*
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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 will be 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 will be developed utilizing monoclonal antibodies recognizing these compounds. This new assay will be validated in a model population, crude coal tar treated psoriasis patients and controls. Blood and urine will be collected from patients and controls. Exposure to BP will also be measured by a panel of previously developed assays including quantitation of white blood cell DNA adducts by immunoassay and [^{32}P] postlabeling and measurement of BP-albumin adducts and serum antibodies to BP-DNA adducts by immunoassay. Urines will be 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 will be correlated with 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 are currently being determined by ELISA utilizing previously developed antibodies against BP diol epoxide modified DNA. These antibodies recognize a number of structurally related PAH diol epoxide adducts and thus provide a general marker of exposure to this class of chemicals. Total hydrophobic adducts are being quantitated with the [^{32}P] postlabeling assay. BP protein adducts are being measured in an ELISA with an antibody recognizing these adducts. Plasma will be tested for the presence of antibodies to BP-DNA adducts by noncompetitive ELISA as an alternate marker of exposure to BP.

In addition to quantitation of urinary levels of BP and its metabolites by ELISA, 1-hydroxypyrene is being measured by HPLC and mutagens in urine

are being determined with the Salmonella typhimurium mutagenesis assay.

In a small subset of patients, skin biopsies were obtained at the time of treatment. PAH-DNA adducts were visualized in frozen sections by immunohistochemical staining with adduct specific antibody followed by fluorescent labeled secondary antiserum. This allowed visualization of adducts in specific cell types. Adducts were also quantitated on DNA isolated from the biopsies by [^{32}P] postlabeling.

Significant Findings

Monoclonal antibodies have been developed against BP and its metabolites from the spleen cells of animals immunized with BP covalently coupled to carrier protein. These antibodies were characterized in terms of sensitivity and specificity by competitive ELISA. The ELISA has a 50% inhibition of antibody binding at 4pmole 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, especially in humans, is unknown. Thus, the assay will provide a relative measure of metabolites present.

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

Publications

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Mechanisms of Cytoskeletal Injury by Ni Compounds

Ken C. Lin
Boston University School of Medicine
Department of Pathology
80 East Concord Street
Boston, Massachusetts 02118

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Importance to Occupational Safety and Health

Nickel (Ni) is a well-documented respiratory tract carcinogen among nickel refinery workers involved in high-exposure operations such as grinding, calcining, sintering, and leaching. Evidence from the British epidemiologic studies showed that nickel refinery workers had a five-fold increase in lung cancer and as high as 150-times increase in nasal sinus cancer compared to the control. Many cases of severe acute and even fatal toxicity have also been reported following nickel carbonyl exposure. Furthermore, Ni is also notorious for inducing nickel contact dermatitis, one of the most common forms of allergic contact dermatitis. Indeed, recent data indicate that Ni accounts for 8% of the cases of occupational dermatitis, which is already the most prevalent occupational disease, and that Ni is the major allergen for women with whom large increases in the number of cases have been reported. Moreover, Ni and its compounds are widely used in a variety of industries including alloys (e.g. stainless steel), electroplating, Ni-Cd battery, electronics, textile production, chemical manufacture, petroleum refining, edible oil hardening, food additive, etc. Thus, the ubiquity of occupational exposure to Ni in workplaces highlights the importance to gain a clear understanding of mechanisms of Ni toxicity and carcinogenesis. With the advent of new insights into cytoskeletal dynamics, more evidence is revealed concerning the association of cytoskeletal changes with a wide variety of human pathological conditions. Moreover, Ni, like several other heavy metals [e.g. Cd(II), Pb(II), As(III)], has been shown to cause severe damage to microtubules, one of the major components of the cytoskeleton. This proposal intends to investigate the possible role of the cytoskeleton in mediating cellular injuries by Ni compounds.

Objectives

The goal of this project is to elucidate the mechanisms by which Ni-induced cytoskeletal perturbation occurs in cultured 3T3 cells exposed to Ni, and its relationship to cell injury and possibly carcinogenesis. Effect of Ni on the *in vitro* polymerization of purified microtubule proteins containing tubulin and microtubule associated proteins (MAPs) will be investigated. The kinetics of polymerization *in vitro* will also be assessed by electron microscopy to detect any changes in morphology of the assembled microtubles. Since MAPs play an important role in the polymerization and stabilization of microtubules, phosphorylation state and distribution of MAPs and their isoelectric variants will also be examined.

Methodology

For the experiments involving *in vitro* microtubule assembly, bovine brain microtubule protein is purified according to the temperature-dependent disassembly/assembly method. Assembly of microtubules *in vitro* is done at 27°C and monitored spectrophotometrically by measuring the increase in turbidity. Continuous recording of turbidity of each experiment is provided by a Perkin Elmer R100A chart recorder connected to the spectrophotometer.

For analysis of MAPs *in situ*, metabolic labeling of 3T3 cells and 2-dimensional gel electrophoresis are employed. Cells are metabolically labelled with [^{35}S]-methionine or/and ^{32}Pi, then selectively extracted with detergent and $CaCl_2$. The extracted fractions are analyzed via 2-D gel electrophoresis as described by O'Farrell.

Significant Findings

To understand the mechanism of the Ni^{2+}-induced MT change, we investigated the effect of Ni^{2+} (0.01 to 3.0 mM) on *in vitro* tubulin polymerization. Ni^{2+} at lower concentrations (0.01 to 1.0 mM) had little or no significant effect on the kinetics of MT polymerization. In contrast, in the presence of 1.5 to 2.0 mM Ni^{2+}, a significant promoting effect on both the rate and the final extent of polymerization was observed. However, at Ni^{2+} concentrations higher than 2.0 mM, such stimulatory effect on the rate and the final extent of tubulin polymerization declined. Furthermore, the promoting effects of Ni^{2+} on MT polymerization were accompanied by a significant decrease in the lag period. Electron microscopic examination of samples of the polymerization product showed that MT, polymerized in the presence of 2.0 mM Ni^{2+}, appeared more numerous and shorter ($1.10 \pm 1.02\ \mu m$) than those of control ($3.81 \pm 2.29\ \mu m$). This was probably a direct result of an increase in the number of initiation centers in the presence of Ni^{2+} as a consequence of the decreased critical concentration (7%) necessary for polymerization to occur. Our results suggest that Ni^{2+} may exert its toxic effect on MT in cultured cells by altering the normal kinetics of MT polymerization.

The profile of MAPs in Ni-treated cells was compared to that of MAPs of control 3T3 cells. The results revealed that the expression of two of the thirteen MAPs species identified in 3T3 cells was consistently enhanced in the Ni-treated cells.

The two MAPs had similar pI (6.8) and apparent Mr of 56 kD and 52 kD. The integrated intensities of protein spots of MAP 56/6.8 and MAP 52/6.8 were increased by 299% and 365%, in Ni-treated cells. The data suggest that the enhanced expression of the two MAPs may play an important role in the formation of the characteristic perinuclear MT bundles observed in 3T3 cells exposed to Ni.

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Stress in One Occupational Group: Teachers

Irvin Schonfeld, Ph.D.
The City College of CUNY
Department of Social
and Psychological Foundations
Convent Avenue and 138th Street
New York, New York 10031

Program Area: *Psychological Disorders*
Grant Number: *2 R01 OH02571-04*
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Importance to Occupational Safety and Health

Teaching is a profession that is critical to the economic and political well-being of the United States. We entrust our children to America's teachers. Teaching, however, is a beleaguered profession (Farber, 1991). Although many urban schools are dangerous places, teachers are exposed to difficulties that are not just limited to the threat of personal violence (e.g., simple disrespect, vandalism). The longitudinal study supported by NIOSH/CDC documents the effects of preventable work-related factors on the psychological well-being of newly appointed schoolteachers.

Objectives

1. To compare the mental health (e.g., depressive symptoms) of recent 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 behaviors (e.g, tranquilizer use) and morale (e.g., job satisfaction) of new teachers.
3. To determine the types of resources, including personal dispositions (e.g., locus of control), social support, and coping strategies, that affect health outcomes in teachers.
4. To study intensively one variety of social resource, namely, social support.

Methodology

Subject recruitment began when potential participants were graduating seniors in colleges that have a record of supplying local education authorities with teachers. Because a great majority of the subjects recruited were women, the findings presented here are limited to women. Participants completed questionnaires in the summer following graduation (Time 0), the following fall (Time 1), the following spring (Time 2), the second summer (Time 3), and so on. The findings are limited to Times 0, 1, and 2. The questionnaires included standard measures of psychological (depressive and psychophysysiologic) symptoms, health behaviors (e.g., smoking, obesity), and measures of the work environment that were specially designed to minimize bias (Schonfeld, in press).

Significant Findings

1. The quality of the work environment was associated with postemployment depressive symptoms but not with preemployment symptoms. A control group consisting of women who obtained full-time jobs outside of teaching tended to have relatively high levels of symptoms during the preemployment period and the two postemployment periods (Times 1 and 2). The women who became teachers and obtained jobs in the "best" schools experienced a pre- to postemployment decline in symptoms. The women who obtained jobs in schools with the greatest exposures to adverse job conditions showed a pre- to postemployment increase symptoms. The depressive symptoms found in women who obtained jobs in schools with intermediate levels of adversity showed no significant change in symptom levels. The findings mitigate against a selection explanation.
2. In multiple linear regression analyses, the quality of the work environment (whether measured by the frequency of events like student disrespect or violence against teachers) was found to exert large effects on fall and spring depressive symptoms, controlling for preemployment symptoms and other potential confounders (e.g. nonwork stressful life events). The work environment also affected psychophysiologic symptoms, job satisfaction, motivation to continue in the profession, tranquilizer use, obesity, self-evaluated health, and self-esteem.
3. Individual coping efforts were not generally related to psychological symptoms when preexisting symptoms were controlled. The main factor apart from school conditions and prior symptoms that affects psychological symptoms was social support. Supportive relationships measured prior to work-force entry mitigated the impact of job conditions on well-being. Support from colleagues exerted different types of affects. Rather than buffering the impact of job conditions on depressive and

psychophysiologic symptoms, colleague support amplified the effects of adverse working conditions. This latter finding suggests that colleagues are exposed to similar conditions and that communications among colleagues reinforce the sense of adversity experienced by the teaching community.

Conclusions. Inspection of the relative effect sizes of the factors affecting the well-being in the teachers indicates that work-environment exposures are paramount. The risk factors involved are preventable. Student violence and generally disruptive behavior can be prevented. Findings bearing on coping behaviors indicate that attempts to change the personalities of teachers in order to reduce job stress are misplaced.

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A Laboratory Model of Sick Building Syndrome

Robert Frank, M.D.
The Johns Hopkins University
School of Hygiene and Public Health
Department of Environmental Health Sciences
615 North Wolfe Street, Room 6010
Baltimore, Maryland 21205

Program Area: *Psychological Disorders*
Grant Number: *1 R03 OH02856-01*
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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 to reduce air conditioning and heating costs by minimizing air leakage through the building envelope. However, concern has arisen that such construction practices may compromise indoor air quality and thereby pose a threat to worker health. The term "sick building syndrome" (SBS) was coined to describe illness complaints that occur in such workplaces and lack a specific etiology as in Legionnaires Disease or hypersensitivity pneumonitis. SBS complaints have been associated with new buildings and renovations, implicating odorous volatile organic compounds (VOC).

Objectives

There have been relatively few attempts to study SBS under controlled laboratory conditions. The objectives of this study are 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. A secondary objective is to develop a method for testing the role of olfaction in modulating the symptoms of SBS.

Methodology

This project has two stages. During Stage 1, we will assemble the different components of the model that are needed for future studies step by step, as follows:

Step 1 will be to measure 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, will be used to calculate total retained dose. The latter together with the post-exposure measurements of respiratory excretion lay the groundwork for toxicokinetic analysis.

Step 2 will be to test whether the rate of sighing can be used to assess symptoms of breathlessness and/or difficult breathing. Inductive plethysmography will be used to measure the sigh-rate along with minute ventilation (V_T, f, V_E) during exposure to selected VOC.

Step 3 will be to develop preliminary data on the possible relationship among the following: ambient concentration of the irritants(s),

conjunctival symptoms, and changes in composition of tear fluid. The irritants will be administered by means of safety goggles modified for this purpose.

Step 4 will be to test the role of olfaction in modulating SBS. We have determined that olfactory identification of acetone, a volatile organic compound, is not prevented by blocking the nares mechanically and inhaling the vapor through a mouthpiece. We plan to investigate the use of a competing inoffensive odor.

Step 5 will be to explore the possible addition to our model of cognitive testing and a method of assessing glucose metabolism in specific brain regions including the neocortex, basal ganglia and cerebellum. We will assess the uptake of ^{18}F-Deoxy-Glucose in the previously specified brain regions. The technique utilizes a dual-probe positron detector that allows a significantly lower dose of radioligand than is required by positron emission tomography (PET).

Step 6 will involve atopic and allergic individuals, with particular reference to assessing changes in composition of the nasal lavage fluid associated with symptoms of nasal irritation.

All of the following steps will involve collection of preliminary data on 3-5 subjects. The subjects will be either healthy non-smokers with no history of SBS, or subjects with a history of SBS that includes symptoms germane to the assay being tested.

During Stage 2, subjects will be recruited for a preliminary study which tests the feasibility of combining the elements that have been developed. Subjects will visit the laboratory on three separate days. Day 1 will be an orientation-preparation day. On Days 2 and 3, measurements on varied parameters (tear fluid, nasal fluid, neurobehavorial tasks, spirometry, respiratory and heart rates, glucose metabolism in CNS, symptoms) will be made before, during, and following exposures to clean filtered air or mixed volatile organic compounds.

Significant Findings

None to date.

Ventilation for Work in Confined Spaces

Richard P. Garrison, Ph.D.
University of Michigan
School of Public Health
Ann Arbor, Michigan 48109-2029

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Grant Number: *5 R01 OH02329-03*
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Funding Level: *$94,989 ($281,328 Cum)*

Importance to Occupational Safety and Health

Accidents during work in confined spaces (CS) have resulted in serious injuries and deaths - roughly 200-300 fatalities each year in the United States. The majority of CS accidents are caused by air contaminants which are either toxic, flammable, or cause oxygen deficiency. There may also be instances of overexposure to airborne chemicals, but very little is known on this issue.

Ventilation is recognized as a primary means of engineering control - a means by which hazardous atmospheres are changed and rendered less hazardous (which administrative controls do not accomplish). Relatively little is known pertaining specifically to CS ventilation design. This lack of knowledge has diminished awareness and emphasis by industry for implementing ventilation for work in confined spaces. It also weakens the ability of agencies such as NIOSH to recommend effective guidelines, and OSHA to enforce safe procedures.

This study is directed toward the need for more knowledge on how to ventilate confined spaces. It will hopefully lead to greater awareness and action to use ventilation and help prevent needless accidents, injuries, and deaths.

Objectives

The overall objective of this project is to advance the state of knowledge of CS ventilation design. More specifically, this study strives to:

1. Observe and evaluate ventilation characteristics of CS laboratory models and describe guidelines for effective ventilation design.
2. Establish an empirical (regression) database that represents the experimental characteristics which can be useful in the development and evaluation of computer models to aid in CS ventilation design.
3. Develop and evaluate computer modeling to approximate contaminant dispersion and ventilation effectiveness in CS models.

Methodology

Laboratory testing investigates ventilation characteristics for different CS model shapes and sizes, ventilation design parameters, and contaminant characteristics. CS model variations have included cubical and noncubical shapes with a single top opening. The noncubical shapes involved expansions, vertically and/or horizontally, from a basic cubical model. Cubical shapes were used to evaluate characteristics of geometric similarity between two models of significantly different size.

Ventilation design parameters included ventilation mode (exhaust vs. supply), volume flowrate (ACH, "air changes" per hour), and inlet/outlet elevation (%H, percentage of CS model height). Studies of contaminant characteristics focused upon recovery from oxygen deficiency caused by gases of different specific gravity (SG): nitrogen, carbon dioxide, chlorodiflouromethane, and sulfur hexafluoride (SG = 0.98, 1.5, 3.0, 5.0, respectively). Characteristics of "trace" (lower concentration) contaminants were tested using isobutylene.

Air samples were drawn from four locations inside the CS models. Analyses involved two primary methods: (1) oxygen deficiency-using a four-channel monitor with electrochemical oxygen sensors, and (2) "trace" characteristics-using a portable gas chromatograph with a photoionization detector. Ventilation flowrates were measured with a calibrated orifice plate.

Experimental data were regressed against an exponential model. The rates of recovery from contaminated to ambient concentrations were represented by recovery time constants, forming an empirical database for CS ventilation design.

Computer models for contaminant dispersion and ventilation effectiveness focused upon a multicellular method which predicted oxygen recovery characteristics reasonably well. Initial estimates of airflow patterns were based upon experimental observation and approximation. Subsequent efforts were made to utilize FEM (Finite Element Method) and BIEM (Boundary Integral Element Method) to model CS airflow characteristics.

Significant Findings

Significant findings from this study include the following:

1. Mechanical ventilation was effective in eliminating oxygen deficiency in a variety of CS model, ventilation, and contaminant situations.
2. Supply ventilation was more effective than exhaust ventilation. CS locations aligned with the supply outlet experienced very rapid oxygen recovery.
3. Inlet/outlet elevation had significant effects upon ventilation effectiveness, with low I/O elevation generally preferable to high.
4. Ventilation time decreased with increasing flowrate, but not always in a simple linear manner, and sometimes with a limit above which increasing flowrate had relatively little effect.
5. Changes in CS model shape had significant, variable, and somewhat inconsistent effects upon ventilation time.
6. Geometric similarity and equal nondimensional flowrate (ACH) were necessary and sufficient for cubical CS models of different size to demonstrate very similar ventilation characteristics.
7. Ventilation effectiveness (oxygen recovery) characteristics varied significantly with contaminant stratification, and oxygen recovery was slower for increasing contaminant SG.
8. A multicellular contaminant dispersion computer model was able to predict ventilation effectiveness reasonably well for situations involving purging, continuous, and variable rates of contaminant release.
9. The BIEM provided reasonably good predictions of velocity characteristics for the multicellular model in the case of exhaust ventilation; predictions were not as good for supply ventilation.
10. Dilution ventilation characteristics for "trace" contaminants were similar to those for oxygen deficiency.

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Fundamental Factors that Affect Dust Generation

David Leith, Sc.D.
University of North Carolina
Department of Environmental Sciences and Engineering
Rosenau Hall, CB #7400
Chapel Hill, North Carolina 27599

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Importance to Occupational Safety and Health

Powders and granulated solids are used throughout industry. Wherever these materials are handled, they generate dust that can affect worker health, cause a safety problem, and cause a nuisance.

Factors that affect dust generation are important but poorly understood. Information about these factors is necessary: (1) to develop product specifications for the dustiness of industrial materials, (2) to assess the inherent dustiness of processes and materials, important for the pre-manufacture notification requirements of TOSCA, and (3) to evaluate changes to materials or processes that can control dust problems.

Objectives

This project addresses these needs by seeking to achieve three objectives:

1. Develop a test that measures dustiness. We developed a method to evaluate the generation rate and size distribution (dustiness) of dusts generated by handling granular materials.
2. Use the test to understand factors that affect dustiness. We investigated quantitatively the dependence of dust generation rate and size distribution on factors that affect dustiness.
3. Evaluate measures by which dustiness can be controlled. Using results from the above, we evaluated means by which industrial dust problems can be controlled.

This research will help characterize sources of industrial dusts and will help develop understanding that allows dust generation to be minimized at those sources. As a result of this research, health and safety problems related to dust exposure will be assessed and controlled more reliably.

Methodology

We have developed a test that measures simultaneously the generation rate and size distribution of dust produced under conditions that simulate handling of granular materials in industry. In this test, material drops at a constant rate from a known height into a hopper with a receiving pile that has constant height. The generated dust is carried to an elutriation column that removes particles larger than 25 μm in aerodynamic diameter. At the outlet of this column is a high-volume cascade impactor that sorts these particles by aerodynamic size. Air entrained with the column of falling material is measured independently with a bleed system. We have conducted experiments to measure the reproducibility of this test procedure, as well as the generation rate and size distribution of an aerosol produced by dropping materials that include sand, limestone, flour, and cement with various drop heights, mass flow rates, moisture contents, and size distributions.

Significant Findings

Results of these experiments showed that this test method gives reproducible results, and that the variables tested here affect generation rate and size distribution with the following order of importance: (1) moisture content, (2) drop height, (3) size distribution, and (4) mass flow rate. Different materials respond to the same test in different ways. These findings can be explained through a balance between the binding forces that keep granular materials together and the separation forces that act when the material is handled. Results from this work are correlated mathematically through an equation that predicts dust generation for particles of given size.

Publications

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Computer Simulation of Push-Pull Systems

Michael R. Flynn, Sc.D.
University of North Carolina
School of Public Health
Environmental Sciences and Engineering
CB 7400 Rosenau, Room 118
Chapel Hill, North Carolina 27599-7400

Program Area: *Control Techniques*
Grant Number: *5 R01 OH02710-02*
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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 e.g., open surface tank operations.

Objectives

The specific objectives are to (1) develop a computer code to solve the three-dimensional continuity and Navier-Stokes equations governing the flow of a hood, jet, and crossdraft; and (2) validate the computer predictions of velocity, capture efficiency, and contaminant distribution with wind tunnel tracer studies.

Methodology

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

Significant Findings

At the present time, three-dimensional finite element codes for the prediction of the velocity field of a laminar square jet have been developed. These codes include the capability to handle the convective term with either a standard Galerkin formulation or an upwinded version. The upwinded version converges about twice as fast as the standard Galerkin form. Computer predictions are in good agreement with published experimental values. Extension of this code to the turbulent square jet and subsequently the basic push-pull configuration are underway.

Experimental measurements of the capture efficiency for a coaxial flanged circular hood and jet in the presence of a perpendicular cross draft have been obtained. In addition, preliminary flow visualization of the jet trajectory with neutrally buoyant tracer bubbles has been undertaken.

Emission Factor Development for Intermittent Workplace Sources

Richard A. Wadden, Ph.D.
University of Illinois at Chicago
School of Public Health
Environmental and Occupational Health Sciences
P.O. Box 6998
Chicago, Illinois 60680

Program Area: *Control Techniques*
Grant Number: *1 R01 OH02804-01*
Start & End Dates: *12/01/90 - 11/30/93*
Funding Level: *$70,140 ($70,140 Cum)*

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, copper and nickel 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 year of the study, we carried out field tests under production conditions on: (1) Three methyl chloroform degreasers in a microcircuit production facility; (2) Three Pb wave soldering lines of different designs in a plant making electronic circuit boards; (3) Cu emissions from an electrolytic copper plating line; (4) Two decorative chrome electroplating lines; (5) A methylene chloride degreaser; and (6) A terpene degreaser using limonene. Preliminary results of several of these tests have shown that our observations are consistent with available (but limited) inventory data.

Significant Findings

The results of this study will provide: (1) A compilation of activity-based emission factors for Cr, Ni, 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

Michael R. Flynn, Sc.D.
University of North Carolina-Chapel Hill
School of Public Health
Environmental Sciences and Engineering
CB 7400 Rosenau, Room 105
Chapel Hill, North Carolina 27599-7400

Program Area: *Control Techniques*
Grant Number: *1 R01 OH02858-01*
Start & End Dates: *07/01/91 - 06/30/94*
Funding Level: *$61,343 ($61,343 Cum)*

Importance to Occupational Safety and Health

This project is designed to bring the methods of computational fluid mechanics to bear on the problem of estimating worker exposure. At the present time the inability to estimate exposure remains a serious deficiency in the design process for contaminant control ventilation systems.

Objectives

The specific objectives are: (1) expand an existing computer code based on discrete vortex methods to predict airflow patterns around a worker and a nearby obstacle; (2) develop predictions of exposure using particle tracking methods; and (3) conduct wind tunnel simulations to validate computer predicted flow patterns and exposure estimates.

Methodology

Significant improvements in parallel and serial algorithms for discrete vortex methods continue to appear in the fluid mechanics literature. These improvements are being integrated into the existing algorithm to improve speed and flexibility. Sulfur hexafluride 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

At present a boundary integral subroutine has been developed and tested to calculate the potential flow around multiple objects in the flow field. This algorithm has successfully replaced the existing submerged panel method in the discrete vortex code, thus improving speed and flexibility. The ability to calculate the potential flow around multiple unconnected bodies in the domain has been developed in order to examine worker interaction with workpieces, machinery etc.

Field Study of Local Exhaust Ventilation Performance

Lorraine M. Conroy, Sc.D.
University of Illinois at Chicago
School of Public Health
EOHS (M/C 922)
P.O. Box 6998
Chicago, Illinois 60680

Program Area: *Control Techniques*
Grant Number: *5 K01 OH00078-03*
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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 eighteen field studies. Three sets of measurements were done during each study to answer the questions asked in the specific aims.

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. Simultaneously with the SF_6 measurements and during operational periods, 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. The duct concentration and the emission rate allows for 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.

Capture Efficiency of Local Exhaust Hoods

Lorraine M. Conroy, Sc.D.
The University of Illinois
School of Public Health, EOHS (M/C 922)
P.O. Box 6998
Chicago, Illinois 60680

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Importance to Occupational Safety and Health

While the recent developments in the design of local exhaust hoods are significant, further research is needed before any of these models become practical. The work reported in the literature to this point, including that of the principal investigator, has been conducted in the laboratory under controlled conditions. The variable of ultimate interest to industrial hygienists is not capture efficiency or capture velocity, but breathing zone concentration of contaminant. Future research must attempt to relate hood capture efficiency with breathing zone concentration for a variety of hood, worker, and extraneous air flow conditions. An important component of improved capture efficiency models must be a better understanding of the nature of the turbulence which characterizes exterior hood performance. Such understanding is important because turbulence affects both hood capture efficiency and the subsequent transport of contaminant to the breathing zone of the worker.

The research outlined here proposes to address this last issue. The turbulence parameters of typical crossdrafts or air flow disturbances were investigated. Existing capture efficiency models developed for uniform crossdrafts will be used as the starting point for new model development. The new models will include the effects of turbulence parameters on the spread of contaminant around streamlines.

Objectives

The broad long-term objectives of any research of capture efficiency of local exhaust hoods should be: (1) to develop usable, practical, and validated models to predict hood performance; (2) to relate hood capture efficiency to workers' breathing zone concentration; and (3) to develop methods of ventilation design to maintain workers' breathing zone concentration below a specified level (e.g., Permissible Exposure Level, PEL, or Threshold Limit Value, TLV). The specific aims of this research project: (1) to investigate the magnitude and turbulence parameters of typical crossdrafts or disturbances to air flow; and (2) to incorporate turbulence parameters into existing capture efficiency models.

Methodology

The first step in this research project is to investigate the turbulence parameters of typical crossdrafts or air flow disturbances. Four different situations are being studied:

1. An obstruction, such as a person, in the hood flow field.
2. A person walking near a local exhaust hood.
3. A draft through a door due to room pressure differentials.
4. A draft created by a cooling fan.

The velocity in each of the situations listed was measured using a TSI, Inc. two-dimensional hot-wire anemometer with high frequency response suitable for turbulence measurements. Bridge voltages were recorded through an analog-to-digital converter on a Toshiba T5200 personal computer. Bridge voltages were converted to velocities using appropriate calibration curves. Turbulence intensity is defined as the square root of the sum of the square of velocity fluctuation divided by the mean velocity. Turbulence scale is determined by performing a fast Fourier transform on the velocity data to get a power spectrum. Examination of the power spectrum reveals the scale of turbulence.

The second step is the development of predictive models for capture efficiency which include the effects of turbulence as well as mean hood velocity and crossdraft velocity. For each experiment, capture efficiency will be measured as a function of distance from the hood while holding hood length, hood width, hood face velocity, crossdraft velocity, and turbulence intensity and scale constant. The results will be used to develop a model for capture efficiency.

Significant Findings

Crossdrafts and other disturbances to air flow can be quantified in the laboratory. Crossdrafts created in these experiments simulate those typically found in industrial settings. Crossdrafts with velocities similar to those measured in the

laboratory will have significant effects on local exhaust hood performance. The ACGIH Ventilation Manual recommends eliminating crossdrafts and other disturbances to flow. This is unrealistic and this research demonstrates that the crossdrafts cannot be ignored. Crossdrafts ranged from 0.45 fps for a mannequin moving at 1 mph to 14 fps near a cooling fan operating at medium speed. These crossdrafts will result in local exhaust hood capture efficiencies ranging from 98% to 35%, respectively. For local exhaust hoods used to control toxic materials, capture efficiencies as low as 35% could have significant adverse effects on workers' health.

Measured turbulence intensities ranged from less than 1% for a draft through a doorway generated by a room pressure differential of 0.0001 in H_2O to 86% for a mannequin moving at 3 mph. The semi-empirical model, published by the principal investigator, for capture efficiency was developed from wind tunnel experiments carried out with turbulence intensity equal to 4.8%. Preliminary experiments showed that increasing the turbulence intensity to 8.5% had a large effect on the measured spread parameter and therefore hood capture efficiency. Given the wide range of turbulence intensities measured for the simulated crossdrafts, models developed at a fixed turbulence intensity will not give accurate predictions of local exhaust hood capture efficiency.

Full Circle Ergonomic Auxilliary Tool Handle

Samuel V. Johnson, Ph.D.
Full Circle Systems
32 Cherry Tree Road
Loudonville, New York 12211

Program Area: *Control Techniques*
Grant Number: *1 R43 OH02780-01A1*
Start & End Dates: *09/30/91 - 03/31/92*
Funding Level: *$49,913 ($49,913 Cum)*

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 is to answer specific questions concerning the detail of the handle design. This research will insure that the new tool handle maximizes its benefit to a variety of users.

Methodology

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

Significant Findings

Although the tests are still in process, the IEMG and force data collected so far indicate that:

1. When using the test handles, subjects can deliver more force and maintain the force longer before fatigue sets in, as compared with control handles.
2. When using the test handles, subjects tend to use the muscles in both hands more evenly, as compared to using the dominant hand almost exclusively on the control handles.

The data collected on video tape so far indicate that:

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.

These findings indicate that the test handle will be important for 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 important for workers who are asked to shift to a new activity, for which they are not prepared physically (e.g., when a maintenance worker who usually mops a floor is asked to shovel heavy wet snow).

Personal Benzene Vapor Detection Device

Mark A. Druy, Ph.D.
Foster-Miller, Inc.
350 Second Avenue
Waltham, Massachusetts 02154-1196

Program Area: *Control Techniques*
Grant Number: *1 R43 OH02906-01*
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 proposal describes the development of a personal wear badge for the accumulated exposure detection of benzene vapor. The badge consists 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 are 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 will 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

None to date.

New Methods for Quantitative Respirator Fit Testing

Klaus Willeke, Ph.D., CIH
University of Cincinnati
College of Medicine
Department of Environmental Health
3223 Eden Avenue
Cincinnati, Ohio 45267-0056

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Importance to Occupational Safety and Health

Several million air purifying respirators are in use in the U.S. A significant percentage of the American workforce is, therefore relying on respirators to reduce the risk of inhaling hazardous industrial aerosols. OSHA guidelines specify respirator fit testing to ensure the workers' safety. Field studies have shown that the laboratory-measured quantitative fit factors relate poorly or not at all to the workplace protection measured during work performance. Fast, reliable, and low-cost fit testing techniques are needed to ensure that the chosen respirator provides adequate protection.

Objectives

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

Methodology

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

Significant Findings

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

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. Further developments, that also consider the flow through the cartridges, are in progress.

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.

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Respirator Performance Model for Particulates

William C. Hinds, Sc.D.
University of California, Los Angeles
School of Public Health
405 Hilgard Avenue
Los Angeles, California 90024

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Grant Number: *5 R01 OH01595-06*
Start & End Dates: *09/23/83 - 08/31/92*
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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 will use human subjects. Facial seal leakage will be measured with a quantitative fit testing apparatus. A polydisperse oleic acid test aerosol with a fluorescent tag will be used. Concentration will be measured inside and outside the mask and compared to that predicted by the model.

Significant Findings

The initial phase of this study included 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 value 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 35%. Use of full-cycle average measurements in WPF studies may underestimate average inhaled concentration by as much as 50%. Protection factors calculated by the computer model may overestimate by 45% inhaled dose for half masks and by 90% for full-face masks.

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. Preliminary results show a reasonable correlation between measured protection factors and model predicted protection factors.

The first series of experiments on the affect of dust loading on filter performance has been completed. A second series is planned using two additional dust particle size distributions. 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 experimental set-up for the evaluation of facial seal leaks in full-face masks is nearly complete and work will begin as soon as the loading experiments are completed.

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Respirator Tolerance

Philip I. Harber, M.D., M.P.H.
University of California, Los Angeles
Occupational Medicine Branch
Department of Medicine, UCLA
Los Angeles, California 90024-7027

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Importance to Occupational Safety and Health

Respirators are vital components of worker protection programs. To encourage use and to avoid adverse effects, their physiologic effects must be understood. A rational basis for medical evaluation of potential respirator users is that it can identify workers at risk of respirator use without inappropriate job discrimination.

Objectives

The physiologic and subjective effects of respirators are evaluated under a variety of use situations employing both actual respirators and surrogates in order to assess the effects of each type of load imposed.

Methodology

Measurements of physiologic and subjective responses are made including respiratory volumes, flows, and pattern. The relationship between personal psychophysical load sensitivity and respirator effects is evaluated using psychophysical methodology. Ambulatory respiratory measurements with respiratory inductive plethysmography permit studies under field conditions to complement the laboratory studies.

Significant Findings

In the past, respirators and users were assessed to determine whether the physical load imposed by the device is so great that the user cannot meet the demand of the added work. The Respirator Tolerance project has demonstrated both empirically and conceptually that respirator design and user evaluation must consider additional effects which determine whether it is tolerable.

The physiologic response to each type of respirator load (alone and in combination) was evaluated, including flow resistance (inspiratory and expiratory), dead space, and pressure biasing (as from pressure-demand SCBA). Inspiratory resistance produces the prominent effects, although the other loads were significant.

The respirator effect on adaptation of respiratory control (to optimize work of breathing or to minimize sensation) was as important as total ventilation. Further studies illustrated that respiratory pattern adaptation is consistent across subjects and across levels of exercise; in addition, respiratory impaired workers showed a consistent response for these variables. Subjective response also correlates with respiratory timing adaptation. Thus, effects on respiratory pattern seem particularly useful for evaluating workers and respirators. Ventilation limitation alone does not explain respirator tolerance at submaximal exercise levels.

The studies of normal volunteers in the laboratory setting were complemented by studies on site in two industrial facilities (a foundry and an aerospace manufacturer). Furthermore, respiratory inductive plethysmography (RIP) was applied (with considerable effort) to respirator research, allowing measurement with actual unmodified respirators and in field activities, which are more similar to real life use. These confirmed and extended the laboratory studies. Use of actual respirators, in addition to laboratory surrogates, provides insight; for example, a powered air purifying respirator produced much less physiologic impact than a standard air-purifying device, but the adverse subjective effects were comparable.

Because the traditional effects on air-flow, etc. do not fully explain differences in tolerances among subjects, additional effects were evaluated. Partitioning of airflow between the nasal and oral routes is changed by respirator use, and absolute resting lung volume changes (FRC) were found to be increased by pressure demand (pressure biasing); both possibly account for poor tolerance. Subsequently, based on a pilot trial suggesting its importance, subjective response was also determined. Inspiratory flow resistance is more important than dead space loading. Pressure bias, as with pressure demand respirators, is also important both physiologically and subjectively.

Personal factors affecting tolerance were also studied. Psychophysical load scaling sensitivity (LSS) is an objectively measured personal characteristic, describing growth of sensation with added resistances. Persons with high LSS tend to have greater subjective discomfort and also adapt a different respiratory pattern (which imposes greater actual loads) than do individuals with lower LSS. Differences in LSS (and consequent maladaptation of respiratory pattern) may partially explain differences in tolerance, even among physiologically normal persons who can overcome the respirator resistance itself. Furthermore, on the average, LSS declines with respirator use, thereby improving tolerance to the imposed load.

A series of subjects with mild-moderate respiratory impairment were studied; the pattern of response was comparable to that of normals. This suggests that the types of variable studied in normals are applicable to the impaired.

A group of industrial users self-classified themselves as tolerant/intolerant. There was a tendency for differences to persist on each of several subjective sub-scales and for the intolerants to have a higher LSS. A combined subjective index was useful for separating the tolerant and intolerants.

Subjective measures may be consistently measured, are related to physiologic response, and reflect two important personal characteristics (LSS and self-rated tolerance). They can distinguish respirator load types and provide complementary information to physiologic measures. The components of subjective response were assessed; perceived limitation of exertion and subjective discomfort may be dissociated. The data suggest that subjective response should be included in evaluations of both respirator designs and specific workers.

Extensive studies showed general comparability of volunteer, mildly impaired, and industrial populations. Field course testing showed results comparable to those of the laboratory and was surprisingly consistent (as judged by test-retest consistency on replicate periods in the same subjects, field studies are as consistent as lab studies for both physiologic and subjective data).

In summary, the project has shown that respirator effects cannot be considered merely as limiting ventilation and maximal exercise. Very important respiratory control adaptation and subjective effects were described, and the project evaluated interrelationships among various respirator loads, exercise level, personal characteristics, ventilatory, sensation, respiratory control, and subjective effects. These factors should be considered when comparing alternative respirators or testing workers. They also explain why some apparently "normal" workers have poor tolerance.

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Respiratory and Thermal Physiology of Face Masks

Arthur B. DuBois, M.D.
John B. Pierce Foundation Laboratory
290 Congress Avenue
New Haven, Connecticut 06519

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Importance to Occupational Safety and Health

Impermeable protective clothing worn in hazardous environments prevents evaporative heat loss, feels hot, and can be worn for a limited time. Devices to carry body heat away restrict mobility and add to the weight and expense. Respiratory protective devices are hot and uncomfortable (Nielsen, et al., 1987; Gwosdow, et al., 1989). However, evaporative cooling of the outer surface has been found to reduce the skin temperature of the face and to improve the comfort of face masks (DuBois, et al., 1990). Early attempts at cooling suits by evaporation of water from wet cloths placed on the outer surface have been promising.

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.

Current objectives have been to extend the concept of evaporative cooling of face masks to include evaporative cooling of impermeable suits, to ascertain the effect on skin temperature and comfort of subjects during moderate exercise, and to extend the period of time chemically protective garments may be worn before the wearer becomes too hot to work.

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. An outer cover made of 1/8 inch thick felt cut and sewn as a hood and jacket, or else Handi-Wipe cloths (a thin, woven fibre, porous, wettable material) was draped over the front, back, and hood of the impermeable jacket. 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. Thermocouples were taped to the skin inside the mask and suit. Skin temperatures were recorded at one minute intervals using an A-D converter and IBM computer. Comfort votes were noted every 5 minutes.

Subjects wearing the suit and mask with dry cloth attached exercised for 30 min on a Monark bicycle ergometer set at 60 watts. They rested for 30 to 40 min with the suit and mask removed, dried off, changed to dry clothing, and exercised for another 30 min period with the cloth on the suit and mask wet.

The Handi-Wipes were weighed before and after exercise to calculate the evaporative heat lost from the outer surface of the impermeable suit.

Significant Findings

Throughout the exercise period, the skin of the front and back of the chest was 2°C cooler when the felt or Handi-Wipes were wet than when they were dry. The subjects also indicated they were cooler and more comfortable when the felt or Handi-Wipes were wet than when they were 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.

The weight lost from the Handi-wipes during exercise was 70 and 154 gm on one subject, 70 grams on another, and 55 grams on a third.

Further steps to be taken in cooling the body will include changing the wall of the vapor tight suit to a more heat conductive material, cooling a larger fraction of the body surface area, increasing air velocity over the wetted surface, and other means to promote heat transfer from inside the suit to the outer surface where heat is lost by evaporation.

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Factors Affecting Respirator Leak Sites and Shapes

Riedar K. Oestenstad, Ph.D.
University of Alabama at Birmingham
School of Public Health
Department of Environmental Health Sciences
UAB Station
Birmingham, Alabama 35294

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Importance to Occupational Safety and Health

Results of this study will expand our knowledge of where respirator faceseals leak and how those leak sites are related to such critical factors as facial dimensions, the brand of respirator, and if the leak sites vary between different fittings and fit test exercises. This information will be useful to persons designing respirator facepieces and to those responsible for selecting and testing respirators for individual users. It will also permit more accurate modelling of respirator leakage by determining the size and one-dimensional shape of faceseal leaks on human subjects. The study will also provide additional information on the phenomenon of airflow streamlining inside respirator facepieces.

Objectives

The specific objectives of the study are to: (1) determine if leak sites and shapes change between the exercises of a quantitative fit test, (2) determine the variation of leak sites and shapes for multiple fittings of the same respirator on the same subject, (3) determine the distribution of leak sites and shapes for different respirators being worn by the same sample of subjects, (4) more accurately define the characteristics of subjects who show evidence of aerodynamic streamlining under the respirator facepiece, and (5) determine the effect of increased breathing rates on the development of airflow streamlining patterns.

Methodology

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

Significant Findings

Activities to date have been directed toward the selection and toxicological evaluation of an alternative fluorescent aerosol which could be nebulized in aqueous solutions, and toward the construction and evaluation of a larger generation and exposure system. These tasks have almost been completed, and it is expected that testing human subjects will be initiated according to the timetable proposed in the initial application.

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. Tinopol CBS-X's solubility (up to 2.5%) will allow sufficient flexibility in controlling the particle size of the test aerosol for the output size characteristics of a given nebulizer.

A new aerosol generating and exposure system has also been installed and evaluated. The mass and size distribution output of three nebulizers have been reviewed, and a RCI (ETEC-type) nebulizer has been tested with the aerosol conditioning system and exposure chamber (Air Techniques System, Model TDA-71, 2.5 m^3 chamber with air lock). The test aerosol produced by a single RCI nebulizer using a 0.05% of Tinopol CBS-X had a mass median aerodynamic diameter of 0.9 μm and a geometric standard deviation of 1.4. By optimizing nebulizer and chamber operating parameters, an aerosol concentration of about 8 mg/m^3 in the chamber has been achieved. It is planned to operate three of these nebulizers in parallel to provide adequate exposure concentrations for the tests with human subjects.

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Adsorption of Vapor Mixtures onto Activated Carbon

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

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Grant Number: *5 K01 OH00087-02*
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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 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 will be used with two different ionization potential lamps, 8.4 and 9.6 eV.

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 are currently being evaluated and initial breakthrough curves are being measured.

Aerosol Penetration Behavior of Respirator Valves

Lisa M. Brosseau, Sc.D.
University of Minnesota
Box 807 UMHC
420 Delaware Street SE
Minneapolis, Minnesota 55455

Program Area: *Respirator Research*
Grant Number: *1 R03 OH02938-01*
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Funding Level: *$18,102 ($18,102 Cum)*

Importance to Occupational Safety and Health

The protection from harmful aerosols afforded by negative pressure air-purifying respirators depends on both the behavior of filters and valves and facepiece fit. It has been hypothesized that the latter is the most significant factor in a respirator's protection. However, respirator valve failure may add significantly to a respirator's reduced protection. No work has been done to demonstrate valve behavior as stressed with cyclic flow over time.

This research will examine aerosol penetration and leak flow through exhalation and inhalation valves from negative pressure air-purifying respirators. New valves from several manufacturers will be stressed with an eight-hour cyclic flow at two workrates. Penetration of five particle sizes between 0.1 and 1 μm diameter will be measured periodically during each test. At the same time, valve leak flow under static pressure will be determined, in a manner similar to that presently used by the National Institute for Occupational Safety and Health for testing respirator exhalation valves.

Used valves will be obtained from respirators which have been worn in industrial work situations, and similar penetration and leak flow measurements will be made. Workrate and usage time will be estimated by observing and interviewing the respirator wearers, and history of use and maintenance will be obtained from the employer's records.

A model to describe particle size-related penetration for a given workrate and leak flow will be developed using measurements of leak area and valve dimensions. Predictions using this model will be compared with results obtained at different workrates.

Valves are important elements of a respirator and their partial failure could severely compromise the protection offered. These experiments will identify initial aerosol penetration characteristics of respirator valves, as well as changes which may occur due to stress over time. Effects of valve model (manufacturer), workrate, and maintenance program will be explored to gain an understanding of the range of possible valve efficacy. Results of these experiments will help in the development of better valve test methods, the design of better valves, and the identification of appropriate valve usage time and maintenance. In addition, these results will assist in identifying the influence of valves on the protection offered by a respirator over time and usage.

An Advanced Respiratory Protective Device

Joseph R. Stetter, Ph.D.
Transducer Research, Inc.
1228 Olympus Drive
Naperville, Illinois 60540

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Importance to Occupational Safety and Health

Air purifying respirator cartridges are used to allow workers to remain in an ambient which contains toxic gases that would be harmful to breathe. Depending on the concentration of the toxic gas and other factors, respirator cartridges may last from minutes to days before they are expended. One of the major problems users face is determining when the cartridge service life has ended. An active-end-of-service-life-indicator (AESLI), that is being developed under this grant, would be placed in the adsorbent bed and would signal the user when the cartridge life was nearing the end.

An AESLI would give greater protection to the user, who would not have to rely on sensory indicators, such as smell. In addition, the AESLI could be used for toxic gases for which there is no sensory warning, regulations permitting. This could lead to the use of air-purifying respirators with many compounds which now require the use of a SCBA (self-contained breathing apparatus). The use of simpler respirators rather than SCBA in the workplace will lower operating costs as well as improve worker comfort and efficiency.

The development of AESLI is of especially great significance today since the TLV's of about 500 compounds have been lowered, and adequate sensory warning is not provided at these reduced levels for many compounds. When an AESLI is available, it will be possible to continue to employ air purifying respirators instead of self contained breathing apparatus (SCBA) in many applications, with the commensurate benefits.

Objectives

The major objective of this research is the development of active-end-of-service-life indicators (AESLIs). The AESLIs must provide an unambiguous alarm to the user when at least 10% of the respirator cartridge life remains unused, and the AESLIs cannot interfere with the operation of the respirator.

Methodology

Microchemical sensors that operate on ultra low power and detect ppm levels of chemical vapors and gases are applied to the problem of detecting toxic vapors inside an active adsorbent bed. The techniques of chemiresistor, fiber optic, electrochemical and piezoelectric micro-sensors are being investigated. The approach is to interface the new micro-sensor technology with existing adsorbent-based protection systems to create prototype respiratory protection devices. The sensors are being evaluated for their intended purpose under laboratory conditions that characterize performance and simulate field conditions.

Significant Findings

1. Low power carbon-based chemiresistor sensors that operate at adsorbent bed temperature have been developed. The sensitivity of the sensors has been improved to about 100 ppm for many organic compound vapors. This type of device has been incorporated into carbon beds, and currently being tested. A joint test at the NIOSH respirator certification facility in Morgantown was conducted.
2. This project demonstrated for the first time ever an AESLI that can be used at PEL levels for styrene and gasoline fumes, two popular filter uses. Depending on the certification procedure for AESLI, we may have the technology to begin commercial manufacture of AESLI systems.
3. A basic model for the response of the sensor has been developed.
4. An optical waveguide for detection of acid gas vapors has been developed.
5. Electrochemical detectors for CO and O_2 have been mounted in respirator equipment and used in field applications, specifically forest fire fighting.
6. TRI is manufacturing a simple, low-cost, handheld instrument (TRI #5000) to detect hydrocarbon vapors. The principal application of the instrument is to determine when carbon filter beds used in solvent recovery operations have been exhausted.
7. TRI is making a sensor for use in monitoring gasoline fumes in leaking underwater storage tank systems (LUST). Phase III market assessment is being performed.

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Human Metabolism of Halothane - Mechanisms of Toxicity

James R. Trudell, Ph.D.
Stanford University Medical Center
School of Medicine
Department of Anesthesia
Stanford, California 94305-5117

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Importance to Occupational Safety and Health

The set of studies with halothane, isoflurane, carbon tetrachloride, dibromoethane, and styrene validate our *in vitro* test system for examining the effects of hepatotoxins. Both dibromoethane and styrene have been targeted by NIOSH because of their occupational exposure. In that we are able to prepare approximately 200 hepatocyte monolayers from a single rat, we have accomplished a national goal of reducing the number of animals sacrificed in research. Our study with the new anti-tumor drug SR 4233 shows that with this *in vitro* assay system, it is possible to propose probable hepatotoxicity based on its chemical structure, and then test for this toxicity in hepatocyte monolayers.

Our studies with neutrophil-mediated cytotoxicity lend support to a mechanism of hepatotoxicity that may have general applicability to many toxic chemicals. Following an acute exposure to a chemical, reactive metabolites are produced that bind to proteins in the liver, and these modified proteins elicit the production of specific antibodies. If a second acute or chronic exposure to the chemical occurs, these circulating antibodies will bind to the surface of hepatocytes that have metabolized the chemical. Then macrophages, attracted by products of lipid peroxidation and activated by immune complexes, will attack the cells that have bound antibodies and attempt to lyse them. Chronic second exposures that are of too low a level to induce lysis will result in persistent attack by activated macrophages. There is evidence that such a persistent inflammation may initiate carcinogenesis. This hypothesis would suggest that persons who incur an initial high acute exposure to a toxic chemical should be tested for circulating antibodies against metabolites of this chemical, and, if present, be warned against re-exposure.

Objectives

We are studying three interrelated aspects of the hepatotoxicity of halothane and related halogenated hydrocarbons: First, the mechanism by which metabolism of halothane or dibromoethane causes acute hepatic necrosis by rapid damage to essential cellular proteins; second, the metabolic pathway by which formation of free radical metabolites of these halogenated hydrocarbons leads to peroxidation of cell membrane phospholipids and how some of these peroxidized phospholipids may be converted into potent mediators of inflammation and activators of macrophages; and third, the induction of antibodies in certain individuals against metabolites of halogenated hydrocarbons to which they have been exposed and the mechanism by which a second acute exposure or continued chronic exposure may cause circulating macrophages to attack liver cells. Of particular importance is how these chronically activated macrophages may initiate carcinogenesis.

Methodology

Rat liver cells were isolated and maintained in monolayer culture for our studies of the acute toxicity of halothane and other agents. These monolayer cell cultures were used as targets for the studies of neutrophil-mediated cytotoxicity. Human neutrophils were isolated from human donor blood, the neutrophils were activated with PMA, and lysis of the hepatocytes was measured.

In a series of studies, the mechanism of production of leukotriene B_4 (LTB_4) in liver cells was studied by isolating LTB_4 with high pressure liquid chromatography (HPLC), confirming its structure with desorption chemical ionization mass spectrometry (DCI-MS), and measuring its activity with RIA.

We have raised antibodies (anti-TFA-RSA IgG) in rabbits against a trifluoroacetylated albumin adduct (TFA-RSA). We have prepared synthetic N-trifluoroacetyl-phosphatidylethanolamine (N-TFA-PE) adducts. We have used flow cytometry to measure binding of anti-TFA-RSA-IgG antibodies to micelles containing N-TFA-PE adducts.

Significant Findings

The individual contribution of halothane metabolism, hepatic enzyme induction, and hypoxia to hepatotoxicity were measured *in vitro* in our hepatocyte monolayer assay system. This study showed that halothane metabolism is an essential factor and that hepatotoxicity is not due to

decreased hepatic oxygenation, as has been suggested by others. In this same study, it was shown that hypoxia and enzyme induction exacerbate the toxicity of halothane, but another inhalation anesthetic (isoflurane) that was used as a control was not toxic. In separate studies, the same *in vitro* assay system was used to measure the effect of hypoxia on the toxicity of carbon tetrachloride, dibromoethane, styrene, and a new anti-tumor agent, SR 4233.

We have previously shown that during metabolism of halothane, hepatocytes produce 5-hydroperoxyeicosatetraenoic acid (5-HPETE), a product of lipid peroxidation. We have developed two sensitive assays for 5-HPETE and leukotrienes. We have now shown that hepatocytes are capable of converting 5-HPETE into leukotriene B_4. This demonstrates that damaged hepatocytes could release powerful chemoattractants, such as leukotriene B_4, that would attract circulating macrophages. This newly discovered ability supports the immune mechanism of hepatotoxicity that is discussed above.

We have shown that stimulated neutrophils are able to overcome the metabolic defenses of hepatocytes and lyse them. Proof of this ability of neutrophils to lyse hepatocytes was essential to our proposal that antibody-mediated attack may be involved in some forms of hepatotoxicity initiated by environmental chemicals.

We have shown that anti-TFA-RSA IgG antibodies bind to N-TFA-PE in phospholipid micelles. The demonstration of cross-reactivity of antibodies raised against a protein antigen with haptenic groups on a phospholipid may be of importance in understanding delayed onset halothane hepatotoxicity. In addition, this mechanism may contribute to immune-mediated cytotoxicity due to a number of other environmental toxins.

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Chromium Distribution and Toxicity in Mammalian Cells

Edwin M. Uyeki, Ph.D.
The University of Kansas Medical Center
39th Street and Rainbow Boulevard
Kansas City, Kansas 66103

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Importance to Occupational Safety and Health

Light microscopic analyses are among those most sensitive in detecting injury to cells. By using computer-aided microscopy (CAM), quantitation of the early injury to cells is possible. These studies provide an early assessment and quantitation of injury to cells by occupational toxicants such as chromate [Cr(VI)].

Objectives

We are conducting a computer-aided microscopy (CAM) study of acute and chronic hepatotoxicity of sodium dichromate injected into mice. Within 6 hours of an ip injection of chromate (25 mg/kg), apoptotic bodies were observed at the epithelial surface of the liver; this is the first such

report of apoptosis as a feature of chromate toxicity. We are therefore comparing the multi-phasic response of the liver to an apoptogen (chromate) and to a necrogen (carbon tetrachloride). Each toxicant generated a unique pattern of response, viz., cell injury/death, inflammation, and repair of the liver. Of the 3 phases, we will experimentally ask: What is the nature of the injury, when does it occur, and where is the location of the injury?

Methodology

Of the techniques used to detect injury in tissues, light-microscopic analyses are among those most sensitive in detecting injury to cells. This sensitivity arises from the ability of such techniques to visually select the "one-cell-among-many" (OCAM) which are "different" from surrounding cells. The major advantages of this technique are that one can identify which cells (OCAM) are affected, describe their characteristic staining pattern, and the regional area of the injury. Currently, batch-processing (biochemical) techniques are used as the putative methodology for toxicology as well as all quantitative biomedical sciences. While these techniques have been valuable in the quantitative evaluation of toxicants, they do not address the methodological problems associated with the analysis of one-cell-among-many: The use of batch-processing techniques, by homogenization or cell dispersal obscures the contribution of different cell types to the measured event/content, as well as the loci of injury.

The main drawback to microscopic or pathologic analyses is that, for the most part, they are descriptive and lack quantitation needed for statistical analyses. The advent of new technologies for the capture, digitization, and storage of light-microscopic images, obtained through the union of the light-microscope with television and computers, has given rise to a new methodology with quantitative rigor.

Significant Findings

Several significant features of sodium dichromate hepatotoxicity, *in vivo*, were observed in mice treated with a sublethal dose (25 mg/kg). Specifically, a regional (focal) response to chromate injection, viz., apoptosis, was observed in periportal regions but not in pericentral regions. Because these apoptotic cells first occur at the epithelial surface of the liver 6 hours post-injection, but not in controls, we suggest these apoptotic cells are early signs of contact injury. Chromate appears to cause regional toxicity, primarily affecting cells in the periportal region.

Ploidy of the liver parenchyma appears to be influenced by several factors; animal age is a major factor. Chromate appears to accelerate the normal process of polyploidization in the mouse liver. This increase in ploidy state occurred in all regions of the liver and was not confined to the periportal region.

We examined the effects of chromate treatment on the PAS staining, as an indication of glycogen content of hepatocytes. Our studies showed that PAS staining was significantly decreased in the livers of mice, 6 hr and 2 days after injection, but not at 1 and 3 days after injection.

We developed an efficient and objective methodology for determining ploidy from histological material. Invariably, there are drawbacks to any procedure for determining ploidy. When working with histological material, many nuclei are incomplete, having been cut during the sectioning procedure. If all nuclei are measured, regardless of sectioning, the resulting distribution of nuclei are poorly differentiated. Discarding incomplete nuclei from measurement tends to disproportionately reduce the percentage of large nuclei which are counted. Measuring relatively thick histological sections minimizes the percentage of unmeasured large nuclei, but increases the percentage of nuclei which cannot be measured because of overlap. This overlap phenomenon leads to an underestimate of the percentage of small nuclei, since (1) unlike octaploid cells, a large percentage of the diploid cells in the mouse liver are binucleate with the nuclei in close proximity to one another and (2) diploid cells are smaller than tetraploid and octaploid cells and thus more closely packed. We found that 12 micron-thick sections provide the best compromise thickness for dealing with sectioning and overlap problems.

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Effects of 27 MHz Radiation on Somatic and Germ Cells

Stephen F. Cleary, Ph.D.
Virginia Commonwealth University
Medical College of Virginia
Department of Physiology, Box 551
Richmond, Virginia 23298-0551

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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.

Methodology

Cell suspensions are exposed for 2 hours to CW or PM 27-MHz or 2450-MHz radiation under isothermal conditions *in vitro*. Viability and morphology are assayed immediately after exposure. Cells are cultured for 1-, 3-, or 5 days and functional assays (i.e., cell proliferation, mitogenesis, DNA, RNA, protein synthesis, sperm viability, and motility, *in vitro* fertilization) are conducted. Cytofluorimetry and dielectric spectroscopy are used to investigate the interaction of RF radiation with the cell cycle using synchronized populations of Chinese hamster ovary (CHO) and HeLa cells.

Significant Findings

A single 2h isothermal (37 ± 0.2°C) exposure to either 27- or 2450 MHz RF radiation induces biphasic dose-dependent alterations in human lymphocyte mitogenesis 3d after exposure, or in DNA and RNA synthesis in glioma (LN71) cells 1, 3, or 5d after exposure. The threshold for RF effects on lymphocytes and glioma is being investigated. Exposure of either cell type to SARs in the range 5-50 W/kg stimulated biosynthetic processes, whereas exposure at >50W/kg suppressed cellular activity. Comparison of the effects of CW versus PM (duty cycle 0.377) 27 MHz RF radiation indicate similar biphasic effects on human lymphocyte activation and glioma proliferation. RF exposure of lymphocytes or

glioma *in vitro* at elevated temperature (39°C) altered proliferation relative to exposure at 37°C. This finding is potentially significant since *in vivo* RF exposures in the work place are known to involve radiation-induced heating in some instances.

Exposure of lymphocytes to either CW or PM 2450-MHz at SARs of 0.5- or 5 W/kg resulted in consistent suppression of lymphocyte proliferation 3 days postexposure. Mean suppression resulting from CW exposure was 8%. Exposure at 5 W/kg resulted in statistically significant suppression ($p=0.05$ for logarithmic transformed data), whereas suppression following exposure at 0.5 W/kg was not statistically significant. Exposure to PM 2450 MHz at SARs of either 0.5- or 5 W/kg resulted in statistically significant suppression (p values 0.0001 and 0.002, respectively). Exposure to PM 27-MHz RF radiation at 0.5- or 5 W/kg resulted in statistically significant suppression with the exception of PM exposure at 0.5 W/kg.

Exposure of glioma to 0.5 or 5 W/kg CW or PM 27- or 2450-MHz RF radiation resulted in statistically significant, time-dependent increases in proliferation. Three days after exposure to CW or PM 2450-MHz RF radiation at 5 W/kg, glioma proliferation was increased 42- or 380%, respectively. Exposure to CW or PM 27-MHz resulted in statistically significant 14- or 50% increases in proliferation respectively. Three days following exposure of glioma to CW or PM 2450-MHz RF radiation at a SAR of 0.5 W/kg there was an 18% mean increase in proliferation, whereas CW or PM 27-MHz exposure, at this same SAR, caused a statistically significant ($p=0.001$) 119% mean increase in 3H-TdR uptake.

Dose-dependent RF-induced shifts in the cycle of synchronized CHO and HeLa cells indicate that the biphasic response results from cycle-specific effects on DNA/RNA synthesis. Maximum sensitivity for RF-induced cycle phase shifts appear to occur during Go/G_1 phase.

A statistically significant reduction in the ability of mouse spermatozoa to fertilize mouse ova occurred following a 1 h exposure of sperm at 37 ± 0.2°C. Recent studies of the effect of 27- or 2450-MHz RF radiation on human spermatozoa, using hamster ova penetration as the dependent variable indicate that human spermatozoa are less sensitive to RF exposure than mouse spermatozoa.

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 ± 0.2°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 μM). 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 (D_2O), or (2) at 39°C. RF exposure at 25 W/kg, in the presence of D_2O, 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 D_2O-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.

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Plasma Proteins: Markers of Chemical Exposure

Ghulam A.S. Ansari, Ph.D.
University of Texas Medical Branch
Department of Human Biological Chemistry and Genetics
Galveston, Texas 77550-2774

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Importance to Occupational Safety and Health

The purpose of this study is to develop biological markers of chemical exposure. The chemical and biological assays thus developed to measure changes in plasma proteins can be used to monitor occupationally-exposed populations. Correlation between the changes in plasma proteins and the medical histories of the occupationally-exposed individuals can be used for medical surveillance as well as for risk assessment.

Objectives

A significant number of people are exposed to a variety of chemicals at work sites which may be responsible for toxic manifestation. Such exposure(s) can bring about changes in plasma proteins in terms of their function, concentration, or covalent modification. These changes, which may be responsible for toxic effects, can be used as markers of chemical exposure. The intent of this research is to develop method(s) which can identify the changes in plasma proteins caused by chemical exposure.

Methodology

Effects of chemical exposure on plasma proteins were studied in terms of their biological activity, concentration, and covalent modification. These changes were measured by using bio- and immunoassays and electrophoretic and chromatographic techniques. Covalent modification was further characterized by peptide mapping and compositional and sequential amino acid analysis. The structure of the modified amino acid(s) was determined by spectral techniques.

Significant Findings

Covalent binding of acrolein to albumin

We have studied the covalent binding of acrolein to human serum albumin. Amino acid analysis showed four new ninhydrin positive peaks. These were identified as lysine and histidine adducts utilizing methods we developed earlier.

The adducts formed as a function of increasing concentration of acrolein was dose dependent between 1 to 10 mM range. The lowest concentration of acrolein used to quantitate the adducts was 1μ mM at an albumin concentration of 1 mg/ml. The effects of acrolein on the ultraviolet absorption and the biological function of the protein to bind fatty acid or 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 bromcresol green. Apparently, the alteration in the secondary or higher ordered structure (unfolding) of albumin did not affect its capacity to bind these ligands. These studies indicate that even substantial covalent modification may not result in the loss of biological activity of albumin.

Rapid Quantitation of Acrolein and Crotonaldehyde Modified Albumin

We developed a rapid and sensitive method for the estimation of acrolein adduct of albumin which can subsequently be used as a marker of acrolein exposure. 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 [3H]-NaBH4 to reduce the aldehyde adduct to corresponding alcohol. The radioactivity was measured after exhaustive dialysis and nmoles of carbonyl function/mg protein calculated. The response was found to be linear. This method is about four fold more sensitive compared to the amino acid analysis method in detecting covalent binding of acrolein to albumin. Although not as reactive, crotonaldehyde (a metabolite of butadiene) had a similar capacity to bind covalently with albumin as acrolein. The efficacy of this method needs to be established under *in vivo* conditions before applied to measure occupational exposure.

Susceptibility to Degradation of Covalently Modified Albumin

Albumin which was covalently modified by acrolein or crotonoaldehyde 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.

This study shows 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, and proteolytic enzymes, as well as under *in vivo* conditions.

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Dose/Response for Styrene Exposures

Stephen M. Rappaport, Ph.D.
University of North Carolina
School of Public Health
Department of Environmental Sciences and Engineering
CB #7400 - Campus
Chapel Hill, North Carolina 27599-7400

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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 genotoxic response 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 employing coconut carbon. Measurement of styrene in the exhaled air employed a new device which collects styrene from 3 L of mixed exhaled air in a tube containing 200 mg of coconut carbon. Both types of samples were analyzed by solvent desorption/gas chromatography. Blood styrene was measured via the head space technique using standard addition and gas chromatography. SCEs were measured by the standard method. Styrene glycol was measured in the blood by extraction followed by derivitization and gas chromatography with electron-capture detection. SO-DNA is being measured by a modification of the ^{32}P post-labeling technique. A new technique has been developed for measuring SO-Hb, which takes advantage of a metal catalyst (Raney-nickel) to selectively cleave SO-cysteine adducts of Hb to yield 1- and 2-phenylethanol, which are subsequently derivitized and measured by gas chromatography with electron-capture detection.

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 ($r=0.73$, $n=48$), and SCEs ($r=0.35$, $n=46$). 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. The relative contributions of smoking and styrene in exhaled air to the total variance in numbers of SCEs per subject were 50% and 31%, respectively. This indicates that styrene exposure below 50 ppm, the current OSHA PEL, contributed to elevated SCEs; such findings of SCEs at these levels of styrene exposure have not been reported before.

We have successfully applied the ^{32}P postlabeling technique to *in vitro* modified samples of nucleosides, DNA, and cells and in selected samples of human DNA obtained from this study. The results clearly show that five SO-DNA adducts have been detected. Recent work has confirmed the identities of these adducts in the *in vitro* modified samples as products of reaction of SO at N^2-, O^6-, N-7-, and C-8- positions of guanine.

The methods for measurement of SO-Hb has thus far achieved a sensitivity of 0.1 nmol of adduct per g of globin. When SO was reacted with whole human blood *in vitro* at SO concentrations between 0 and 318 nmol/mL a significant linear correlation ($r^2=0.94$) was obtained suggesting that the production of adducts was proportional to the concentration of SO over this range.

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Hydrocarbon Exposure and Chronic Renal Disease

Nabih R. Asal, Ph.D.
University of Oklahoma at Oklahoma City
Health Sciences Center
801 NE 13th Street
Oklahoma City, Oklahoma 73190

Program Area: *Other Occupational Needs*
Grant Number: *5 R01 OH02391-03*
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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 is to investigate the role of chronic exposure to hydrocarbons in causing chronic renal disease.

Methodology

An ongoing population-based case-control study will be conducted utilizing patients and controls identified from the major counties in Oklahoma. Cases will include all adult patients between the ages of 18 and 79 with chronic renal disease (both those with ESRD and those not yet at that stage) having a confirmed diagnosis of idiopathic chronic glomerulopathy (ICG) as their primary disease and patients with chronic renal failure who have an unknown primary disease. Minimum criteria for diagnosis of ICG will include either a histologic diagnosis or the presence of unexplained proteinuria exceeding 2 gms/24 hrs. All new cases diagnosed between January 1, 1985 and July 31, 1992 meeting these criteria will be included in the study.

A general population-based control group matched to the cases by sex and age (±5 yrs) will be selected from the same communities by a Random Digit Dialing technique.

A detailed questionnaire will be administered to cases and controls. The questionnaire will include information on medical history, family history of chronic renal disease, medication history, smoking and beverage use, life-time occupational history specific for hydrocarbon exposure, demographics and other pertinent data.

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

The statistical minimum number of total cases and controls will be 300 each. The project target number is 500 of each. The study began on September 15, 1989 and will continue for three years.

Significant Findings

None to date.

Permeation of Glove Materials by Organic Solids

James K. Hardy, Ph.D.
University of Akron
College of Arts and Sciences
Department of Chemistry
Akron, Ohio 44325

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Funding Level: *$39,242 ($89,051 Cum)*

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 steadystate 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 I). 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 I. BT Comparison for Direct Contact and Vapor Phase Transfer.

			Phenol	p-dichlorobenzene	
	Distance	Direct	Vapor	Direct	Vapor
Latex	1 cm	10.4	19.5	5.2	8.0
PVC	1 cm	10.6.	15.0	5.2	5.8
Nitrile	1 cm	185	320	ND	ND
Urethane	1 cm			3.6	10.5
	2 cm				11.7
	3 cm				12.0
Neoprene	1 cm	21.0	60		
	2 cm		49		
	3 cm		79		

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 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.

Publications

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Selective Real-Time Detection of Olefin Gases and Vapors

Edward T. Zellers, Ph.D.
University of Michigan
School of Public Health
Department of Environmental
and Industrial Health
109 South Laboratory
Ann Arbor, Michigan 48109-2029

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Grant Number: *5 R01 OH02663-03*
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Importance to Occupational Safety and Health

The study focuses on several olefins and diolefins that have been associated with carcinogenic, neurotoxic, and/or adverse-reproductive health effects. Due to the presence of other organic-vapor contaminants in

industrial settings where these chemicals are used, real-time measurement of airborne concentrations with current personal direct-reading instruments is often not possible. The sensitivity and selectivity provided by the proposed microsensor-based instrument will permit collection of more accurate personal exposure data for each of the target gases and vapors.

Objectives

The goal of this research is to develop microsensor-based instrumentation for selective real-time measurement of each of a series of olefin or diolefin gases and vapors in the presence of common industrial co-contaminants. The primary focus will be on the detection of styrene, ethyl acrylate, acrylonitrile, 1,3-butadiene, β-chloroprene, vinyl chloride, and vinylidene chloride. Although, data relevant to monitoring other toxic olefins will also be obtained. The instrument will employ one or more surface-acoustic-wave (SAW) sensors as the detection element(s). Selectivity for given target compounds will be achieved by coating the sensor surface with one of several regenerable trapping agents.

Methodology

A series of trapping agents will be synthesized and tested for reactivity with each of the specified olefins/diolefins. The trapping reagents will comprise several platinum-olefin coordination complexes of the general formula trans-PtC12(amine)(olefin), and related polymer-bound complexes, designed to react (via substitution of the initially bound olefin) specifically with the target olefin/diolefin. Subtle changes in the electronic and steric properties of the amine and olefin ligands in the reagent should allow for optimization of selectivity toward each of the target compounds in the presence of other potentially interfering chemicals. It is expected that post-exposure regeneration of the original trapping reagents will be possible *in situ* by simple chemical treatment.

The coated sensor(s) will be incorporated into a compact prototype instrument equipped with data-storage and digital-readout capabilities for both real-time and time-weighted-average measurements. Instrument performance will be evaluated in the laboratory with respect to several relevant operating parameters.

Significant Findings

Real-time measurement of ethyl acrylate, styrene, and vinyl acetate vapors at low-ppm concentrations in the presence of each of several non-olefin solvent vapors has been achieved using a 30-MHz SAW sensor coated with a mixture of trans-$PtCl_2$(ethylene)(pyridine) and poly(isobutylene). Use of the related reagent complex $PtCl_2$(1-hexene)(pyridine) permits selective measurement of 1,3-butadiene below 0.3 ppm. In all cases the reagents can be regenerated by exposure to the initially complexed olefins. Acrylonitrile can also be measured using the 1-hexene complex with a calculated detection limit of 4 ppm. Replacing pyridine by 2,6-dimethylpyridine in the 1-hexene complex precludes reaction with styrene but still allows sensitive detection of acrylonitrile and butadiene. Preliminary testing of a 52-MHz SAW sensor with ethyl acrylate has shown a 3.4-fold increase in sensitivity relative to the 30-MHz device. Similar improvements in sensitivity are expected for the other target compounds.

Selectivity for the target olefins/diolefins in the presence of other olefin gases and vapors has been attributed to steric and electronic factors favoring the target olefins. A systematic investigation of steric factors affecting selectivity has revealed that the position and geometry of substituents on the olefin vapors is very important in determining the sensor response. A remarkably high degree of selectivity is found for unhindered olefins. For example, ethyl acrylate can be monitored without interference from its isomers methylmethacrylate and methylcrotonate due to the presence of the methyl groups on the double bonds in the latter compounds. Similarly, the response to styrene is about 10 times higher than that for α-methylstyrene.

Electron withdrawing substituents on the olefins reduce or preclude reaction with the trapping reagents. Thus, the compounds mentioned above can be monitored selectively in the presence of vinyl chloride and vinylidene chloride and no response is observed for trichloroethylene or dichloroethylene. Synthesis of a related class of trapping reagents is currently underway that should permit preferential detection of these electron-deficient olefins.

A prototype battery-powered dual-SAW instrument has been designed and is currently being constructed. The instrument will provide real-time output of olefin vapor concentrations as well as datalogging and coating-regeneration capabilities.

Publications

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Theory and Evaluation for a Workplace FTIR-ROSE Monitor

Steven P. Levine, Ph.D.
University of Michigan
School of Public Health
Department of Environmental and Industrial Health
1420 Washington Heights
Ann Arbor, Michigan 48109-2029

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Grant Number: *5 R01 OH02666-02*
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Importance to Occupational Safety and Health

This project concerns the development and application of open path FTIR technology to workplace air monitoring. In the 1970's, the investigation of remote sensing of emissions (ROSE) using open IR beam paths (OP) for air monitoring was initially reported. Such a system could be used for real-time monitoring of almost all gases and vapors, and particularly of labile or polar compounds that could not be monitored easily by conventional methods. Furthermore, since the ROSE system does not use sampling pumps, lines or a gas sample cell, the usual recovery studies do not have to be performed. In addition, the system is very fast, with a maximum data acquisition rate of as high as two analyses per second.

In the 1980's, the use of FTIR-ROSE was first explored as a technique for remote sensing of chemical warfare agents in the air over a battlefield. In the last few years, several groups have experimented with ROSE for sensing of pollutants at hazardous waste sites. The first such study at a hazardous waste site was a joint effort in 1987 between the EPA and our group. We propose to evaluate our results in the light of this application, and applications at traditional industrial sites, and in the context of the NIOSH Respirator Decision Logic. Therefore, the development and validation of the ROSE method is justified by the use of respirators at industrial sites, and to protecting personnel at hazardous waste sites. The OP design of the system means that it will be as effective for labile and/or polar compounds as for the "traditional" volatile organics for which many monitoring systems are designed. With the availability of such systems, the appropriate level of respiratory protection may be chosen based on real data, rather than on default, worst-case assumptions.

Objectives

During the first two years of this NIOSH sponsored project we have addressed the questions of ROSE-FTIR instrument use: (1) under controlled conditions of varying temperature and humidity, (2) under controlled conditions simulating the workplace, and (3) in the workplace.

All of these tests have been directly related to the situation where there is a slowly varying analyte concentration field, and path-averaged beam results were well-correlated with TWA continuous monitor results. In the most recent test, the relationship was investigated between detection of a chemical leak at a work station, and signalling the need for an appropriate level of PPE.

Methodology

Tests of the FTIR-ROSE system were performed at the General Motors Research Center in an exposure chamber in which temperature, humidity, and air contaminant concentration could be tested; at the University of California, Berkeley, in a large exposure room in which air contaminant concentration could be modeled with the aid of a 3-D sonic anemometer, and monitored using the IR beam and a multi-point conventional monitor. In addition, a field trial was performed at Abbott (pharmaceutical) Laboratories, Chicago, IL.

Significant Findings

An integral part of the development of FTIR-ROSE in the present environment must be concerned with the nature and utility of the data produced by this technology. In the first two years of the project we have come to understand that there is a fundamental difference between the OP-FTIR system used in a fixed beam path mode, akin to fixed position area monitors but delivering a spatial average concentration, and a moveable or multiple beam mode, the latter of which is capable of delivering information on spatial distribution of contaminants in the work space.

We have explored, both theoretically and experimentally, the fixed beam application. In general, we have concluded that fixed beam geometries can offer only conservative upper bounds on personal exposures of workers along the beam path. Note that this objective differs from the idea of tomographic reconstruction of concentration fields in that the objective in the tomographic application is, to some extent, a throw-back to an earlier era where exposure data required both a specification of a time-stationary concentration field and an assessment of worker mobility patterns. To identify and exploit the particular advantages of OP-FTIR are the purposes of this research.

Company Characteristics and Medical Screening of Workers

Leslie I. Boden, Ph.D.
Boston University School of Medicine
80 East Concord Street
Boston, Massachusetts 02118-2394

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Importance to Occupational Safety and Health

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

Objectives

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

Methodology

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

Significant Findings

None to date.

Measurement of Alkenyl/Epoxy DNA Adducts by GC-MS

Roger W. Giese, Ph.D.
Northeastern University
College of Pharmacy
Section of Medicinal Chemistry
360 Huntington Avenue
Boston, Massachusetts 02115

Program Area: *Other Occupational Needs*
Grant Number: *1 R01 OH02792-01*
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Importance to Occupational Safety and Health

It is important to measure DNA adducts in human samples. DNA is an ultimate target in the body for carcinogenic and mutagenic chemicals. Measurements of DNA adducts can help to sort out some of the uncertainties arising from exposure of individuals to multiple chemicals. For example, individuals vary in their metabolism and lifestyle

related to chemical exposure. Detection of DNA adducts can be important even in the absence of knowledge about the genotoxicity of the adducts. This is because of the potential to identify the exposure chemicals in complex mixtures that we need to worry the most about. 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 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) electrophoretically derivatize the adducts; and (4) detect the electrophoric products by gas chromatography-electron capture negative ion-mass spectrometry (GTC-ECNI-MS). Electrophoric derivatization/GC-ECNIMS has been selected because of the need for sensitive, definitive measurements. Current methodology is limited in these respects, which makes it difficult to make accurate assessments of exposure and risk.

Significant Findings

To date an analytical procedure has been designed and partly set up for the measurement of N7-(hydroxyethyl)guanine(7-HEG), the major ethylene oxide DNA adduct. In this procedure, the 7-HEG is first converted by nitrous acid into a corresponding xanthine, and the latter is then derivatized with pentafluorobenzyl bromide prior to detection by GC-ECNI-MS. Both reactions have been established to work independently down to the mid-femtomole level to date. Currently, we are working on coupling the two reactions before we extend the method to lower analyte levels.

We have also worked on extending the sensitivity for detecting the final product as a standard by GC-ECNI-MS by using unusual conditions in the instrument. This has boosted our sensitivity by 10-fold for this compound. Thus, we are now able to detect 1.3 attomoles of the compound as a diluted standard at a signal to noise ratio of 10. The novel conditions that we developed have been written up and accepted for publication.

Publications

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Assessment of Occupational Exposure to Aflatoxin

Mustafa I. Selim, Ph.D.
The University of Iowa
College of Medicine
Preventive Medicine & Environmental Health
108 AMRF - Oakdale Campus
Iowa City, Iowa 52242

Program Area: *Other Occupational Needs*
Grant Number: *1 R01 OH02857-01*
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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 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 alarming levels of aflatoxins in the corn crop. Our preliminary study indicates once detected, aflatoxin B_1 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 major objective of this proposal is to determine the average yearly exposure of farmers to aflatoxin B_1 in airborne grain dust from repeated low level exposures during various on-farm grain

handling activities. This objective 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 B_1 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 presence of small amounts of organic solvents as fluid modifiers, followed by off-line analysis of the extract. Currently, an on-line extraction and analysis procedure are being developed. Anticipated 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).

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 developed and optimized for the detection of fumonisins in grain dust at subnanogram level per sample. Both the aflatoxin and fumonisin methods are off-line extractions with SFE followed by HPLC analysis. Further improvement in sensitivity for both compounds is anticipated by combining the SFE method with HPLC/MS for on-line analysis, which is currently under development.

Publications

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Minimizing Dermal Exposure to Pesticides in Greenhouses

Richard A. Fenske, Ph.D.
Rutgers University
Department of Environmental Sciences
P.O. Box 231
New Brunswick, New Jersey 08903

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Funding Level: *$31,543 ($95,968 Cum)*

Importance to Occupational Safety and Health

Greenhouse applicators are likely to receive substantial dermal exposure during the spraying of pesticides. Few studies have characterized such exposure patterns carefully. The use of a fluorescent tracer allows visualization of exposure patterns and can assist both investigators and workers in determining the causes of exposure and the means for reducing such exposures. It is important to identify factors unique to greenhouse applications which affect dermal exposure.

Objectives

1. Identify the major variables influencing exposure during pesticide handgunning applications in greenhouses.
2. Evaluate the performance of protective clothing under normal application conditions.
3. Determine the effect of ventilation on dermal exposure during applications.
4. Determine the ability of fluorescent tracer evaluations to categorize worker exposure patterns and reduce exposures through education.

Methodology

A fluorescent tracer was introduced into pesticide spray mixes prior to applications. Workers conduct normal application activities and are examined subsequently under longwave ultraviolet light in a mobile laboratory. Patterns of dermal fluorescence were detected and quantified by a video imaging system. An exposure score was assigned based on visual observations. Key factors believed to influence dermal exposure were varied under controlled conditions; e.g., ventilation system and type of protective garment worn. Dermal patches were attached to the inside and outside of clothing to provide an evaluation of spray deposition and clothing penetration independent of the imaging system and visual observations. Patches were extracted in the laboratory and levels of the fluorescent tracer were determined by fluorometry.

Significant Findings

The most significant findings were as follows:

1. Major variables influencing exposure were (a) ventilation system type and status, (b) experience level of applicator, (c) worker's concerns regarding exposure, (d) potential for contact with treated or wet foliage, (d) type of protective clothing worn during application, and (e) reuse of protective clothing.
2. Clothing normally designated as "chemical-resistant" can experience substantial breakthrough within a one-hour application period if the clothing becomes wet by direct and repeated contact with treated foliage.
3. Ventilation systems which produce directional air movement reduced aerosol deposition on skin surfaces substantially during high pressure (200 psi) spraying when applications were conducted by well-trained workers (compared to applications with no ventilation). Exposure was not reduced and in some cases increased by the same ventilation when applications were conducted by inexperienced workers.
4. The categorization of exposure patterns by visual scoring corresponded well with quantitative analysis of fluorescent tracer deposition on skin. The ability to see exposure patterns through fluorescent tracer visualization led workers and greenhouse managers to adopt more careful pesticide use practices; e.g., greater care in handling and application, and purchase of appropriate protective garments.

Hepatic Steatosis and Solvent: A Case-Control Study

Michael J. Hodgson, M.D.
University of Pittsburgh
School of Medicine
190 Lothrop Street #149
Pittsburgh, Pennsylvania 15261

Program Area: *Other Occupational Needs*
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Funding Level: *$26,852 ($56,427 Cum)*

Importance to Occupational Safety and Health

Liver disease is the tenth leading cause of death and the ninth leading cause of years of potential life lost before the age of 65. Although documented and potential hepatotoxins are frequently used in the U.S., outbreaks of occupational liver disease occur only infrequently. Sporadic cases of toxic liver disease are recognized only rarely. Other risk factors, such as obesity and diabetes, have been implicated, although cause of relationships are as yet unclear. Physicians are generally unaware of the various risk factors, unaware of implications of work exposures, and unaware of appropriate diagnostic or therapeutic consequences.

Objectives

1. To estimate the risk for liver disease resulting from alcohol, obesity, and solvent exposures.
2. To develop educational materials for practicing physicians.

Methodology

Case-control study of fatty liver disease (FLD)

Population: All cases of fatty liver disease referred to seven gastroenterology groups in Allegheny County over a two-year period with biopsy-proven FLD were eligible as cases. As controls, age- (within five years) and gender-matched controls were selected from participating GI clinics.

Exposure assessment: Alcohol consumption, obesity, and solvent use were quantified for four time points, i.e., at examination, at diagnosis, maximum usual consumption, and average. Solvent exposure was quantified with ordinal scales of

frequency, intensity, and duration. Specific exposures to pesticides, drycleaning fluids, paint strippers, and spot removers were also identified.

Statistical Analysis: Statistical methods for matched data were used.

Case-control study of risk factors for liver disease

Population: All cases of liver disease seen by one physician at a university hospital from 1/1/88 to 12/31/88 were selected independent of diagnosis. Two control series were identified, both matched on age (within five years) and gender. A first series was selected from university GI clinics and a private gastroenterologist with a similar demographic profile of patients. A second series was obtained by random digit dialing.

Exposure assessment: Alcohol consumption, obesity, and solvent use were quantified for four time points, i.e., at examination, at diagnosis, maximum usual consumption, and average. Solvent exposure was quantified with ordinal scales of frequency, intensity, and duration. Specific exposures to pesticides, drycleaning fluids, paint strippers, and spot removers were also identified.

Statistical Analysis: Statistical methods for matched data are being used.

Re-analysis of NHANES II data

To test the importance of the identified risk factors in a population-based study, the NHANES data set is being analyzed to examine the influence of obesity, recent and chronic alcohol consumption, diabetes, and occupational exposures on liver function.

Exposure assessment: Usual coded data from NHANES were used, including body mass index (weight/height squared), diabetes (questionnaire definition), recent and usual alcohol consumption in ounces per week, and occupation. Occupations were coded as exposed/unexposed on the basis of a review of the literature and occupations identified from the case-control studies.

Statistical analysis: Statistical methods for cross-sectional data are being used.

Significant Findings

Fatty Liver Disease

The study was terminated prematurely because individuals with FLD by sonogram or CT scanning techniques were potentially no longer being biopsied unless they had exposures identified. Apparently, biopsy habits in the gastroenterology community have changed. The study was discontinued to prevent ascertainment bias, and the last two cases were discarded.

The results suggest that obesity and occupational exposure to animal hepatotoxins (OR = 4.5) were independent risk factors for the development of fatty liver disease. No evidence for multiplicative interaction was documented in logistic models. This may have to do with the relatively small sample size or with the lack of such an interaction. When the variable "alcohol consumption" was re-coded from a value of "4 ounces per day" to "any alcohol," alcohol consumption *per se* constituted a third independent risk factor.

Anecdotal evidence (case series) suggests that 1,1,1-Trichloroethane should be reconsidered as a potential human hepatotoxin.

Chronic Liver Disease

One hundred forty-eight (148) cases were identified through the selected mechanism. This represents less than 20% of the cases evaluated at the institution during that time in question, indicating some failure of the method. For 14 cases, no matched controls could be identified; for 3 no diagnosis was recorded in the chart, or the chart could not be found.

No statistically significant associations between individual forms of liver disease and solvent exposures were seen. With telephone controls, mildly elevated risks of two to three-fold were seen in comparisons of autoimmune liver disease and cryptogenic cirrhosis.

NHANES Data

Not yet available.

Publications

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Ethical Decision-Making in Occupational Settings

Bonnie Rogers, Dr.P.H.
University of North Carolina
School of Public Health
CB #7400
Chapel Hill, North Carolina 27599

Program Area: *Other Occupational Needs*
Grant Number: *5 K01 OH00072-03*
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Importance to Occupational Safety and Health

It is well known that workers are exposed to a variety of occupational hazards (e.g. biological, chemical, physical hazards) and many of these workers i.e., pregnant women, may be particularly vulnerable. Issues related to risk of exposure to hazardous substances, right-to-know, workplace discrimination, screening without informed consent, invasion of privacy, lack of confidentiality, whistleblowing, use of incentives to entice the worker to accept risk, and lack of adequate protective equipment are but a few problems that create ethical issues for health care professionals. This study has identified several ethical dilemmas that occupational health nurses (OHNs) find themselves grappling with but without satisfactory resolution. Decisions regarding these problems have far reaching consequences for the health and well-being of the American workforce. Recognition of ethical problems and development of appropriate actions within an ethical framework will help guide policy development. In addition, discussion of these issues and approaches should be encouraged within occupational health curricula.

Objectives

The purposes of the proposed research were to: (1) identify and develop an inventory of recurrent ethical dilemmas experienced by OHNs; (2) develop and administer an instrument to measure occupational health nurses' actions responsive to each dilemma; and (3) determine if specific variables, i.e. type of employment, work experience, educational level, and support systems, were associated with nurse responses to dilemmas. The ultimate goal of this research is to identify nursing actions which are beneficial to workers in helping to resolve ethical dilemmas in occupational health.

Methodology

Phase I, the descriptive study (completed), was designed to develop and provide an inventory of recurrent ethical dilemmas experienced by a representative sample of practicing OHNs through use of a four-round Delphi technique. Identified dilemmas were categorized by a nurse ethicist to delineate recurrent dilemmas and then rated by OHNs as to the importance and impact of the dilemma.

In Phase II, practicing OHNs representing geographic regions of the country developed nursing actions responsive to each ethical dilemma. These actions were evaluated, by nurse ethicists, as to their relative congruence with the Code of Ethics. An instrument containing the 20 ethical dilemmas and related nursing actions was pilot tested on nearly 40 OHNs representative of large/small industries and hospitals for reliability, validity, and clarity. Subjects were asked to specify actions as being both realistic and ideal.

In Phase III, the instrument (20 separate ethical dilemmas) was administered nationally to more than 300 practicing OHNs to measure their responses to ethical dilemmas. Descriptive analyses of nursing actions across dilemmas were conducted. Responses were analyzed for each dilemma on actions as idealistic versus realistic behaviors. Information will be disseminated through publications and conferences.

Significant Findings

Phase I of the study, identification of the most pressing and recurrent ethical dilemmas in occupational health settings experienced by OHNs, was completed through use of a four-round Delphi technique procedure. In this phase, nearly

400 descriptions were received from 137 respondents. A consensus on concerns of the most important problems was reached. Ethical dilemmas were categorized by nurse ethicists from the incidents themselves, from the general bioethics literature, other surveys of ethical problems/dilemmas in nursing, and the Code for Nurses.

The categorical placement of the dilemmas sometimes fell under more than one category. An example would be situations that could be categorized as both "right-to-know" and "truthtelling" or an underlying concern for avoiding/preventing harm and respecting autonomy. These were categorized according to what was considered to be the primary ethical problem. Dilemmas were categorized into the following areas: Interests/Welfare of Individual vs. Interest/Welfare of Group or Company; Truthtelling/Lying, Deception; Respect of Autonomy; Justice and Equity; Employee vs. Employer Right-to-Know; Incompetent, Unethical, Illegal Practice of Health Care Professionals; Protection of Confidentiality/Respect for Privacy; Whistleblowing; Loyalty/Obligation to Employer. Using these categorical themes, an instrument was designed which contained 48 recurrent ethical dilemmas representing these categories. Utilizing the Delphi procedure, the 48 ethical dilemmas were rated on three successive rounds and group means were calculated for each variable, importance to the profession and impact on worker health.

In Phase II of the study, the scores for the 48 ethical dilemmas were reaveraged and dilemmas with combined average scores (for importance to the profession and impact on worker health) of at least 6.00 (on a 7.00 scale) were determined to be the most pressing problems. This resulted in a total of 20 ethical problems to be used in the Phase II Ethics Workshop held in Chapel Hill, North Carolina on November 9-11, 1989. Twenty-three individuals from across the country participated in the workshop to discuss and develop alternative strategies to address the dilemmas. Final strategies were developed for each dilemma discussed, and an instrument to measure nursing actions was developed for each of the 20 dilemmas. Dilemmas and strategies developed were then rated by nurse ethicists as to appropriate ethical responses.

In Phase III, all dilemmas were pilot tested on nearly 40 randomly selected OHNs. Test-re-test reliability was also completed. Pearson coefficients ranged from .64 to 1.00 on the dichotomous variable with 16 dilemmas having r = .83 or greater. Pearson coefficients for the Likert scale variable ranged from .65 to .99 with only one dilemma having a coefficient below .81. Modification of wording was made to further clarify the intent of items with lower r values. The final instrument was then mailed to 353 randomly selected subjects (geographically divided) from the AAOHN mailing list. Responses were received from 191 subjects with 88% working in traditional industry settings. Each subject rated approximately seven separate dilemmas (randomly assigned) on both realistic and idealistic behaviors for each nursing action. For all dilemmas, discrepancies were apparent between what the nurse would do contrasted with what should be done. Often nurses chose the category "uncertain" as to what should be done. Space does not permit a description of results for each dilemma; however, a full description of each separate dilemma can be found in the final report.

An ethical-decision making model has been developed and can be useful in discussing ethical problems and resolutions and in effecting policy decisions. In addition, using this model as an educational strategy in academic and continuing education environments, will be helpful to practitioners in discussions about ethical principles and their application to actual problems.

Publications

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Safety, Industrial Relations, and Productivity

James C. Robinson, Ph.D.
University of California, Berkeley
Institute of Industrial Relations
2521 Channing Way
Berkeley, California 94720

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Grant Number: *5 K01 OH00075-03*
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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

Edward T. Zellers, Ph.D.
University of Michigan
School of Public Health
Department of Environmental and Industrial Health
109 South Observatory
Ann Arbor, Michigan 48109-2029

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Grant Number: *5 K01 OH00077-03*
Start & End Dates: *07/15/89 - 07/14/92*
Funding Level: *$27,251 ($90,878 Cum)*

Importance to Occupational Safety and Health

This work addresses the need for improved sensor technology in personal direct-reading monitoring equipment for organic vapors. Currently available instruments generally lack the selectivity necessary to identify a given vapor or to discriminate between the components of even simple mixtures of vapors. The successful project will yield an array of sensors capable of identifying organic vapors from several classes and differentiating the components of vapor mixtures. The small size and low power requirements of the array will facilitate incorporation into miniaturized instrumentation suitable for use in real-time personal monitoring and respirator-cartridge breakthrough applications. This, in turn, will improve capabilities for characterizing and controlling occupational exposures to hazardous chemicals.

Objectives

This study concerns the development of an array of coated surface-acoustic-wave (SAW) microsensors for the measurement of organic vapors. The microsensor array comprising sensors with partially selective responses is intended to provide response patterns that are characteristic of different vapor contaminants. Pattern recognition analysis of the multidimensional sensor-response data can then be used to determine the identity and quantity of the target vapor(s) when present alone or in mixtures with other vapors.

Methodology

A series of chemically sensitive SAW-sensor coatings will be tested for their responses to several members of each of 11 classes of organic vapors. The sensor responses will be stored and then analyzed collectively using pattern recognition methods. Following initial screening experiments a subset of coatings will be chosen based on their ability to discriminate between different types of organic vapors. The coating materials will consist of monomeric, oligomeric, and polymeric compounds with differential absorption affinities for organic vapors. Exposure of the sensor to industrially relevant vapor mixtures will be performed to verify the results predicted from the pattern recognition analyses.

Significant Findings

Sensor responses have been characterized for 15 coatings. Six of these have been tested for each of 40 vapors from 11 chemical classes. Three coatings were unstable and not investigated further. Testing of the six remaining coatings is still in progress. Preliminary analyses indicate that with a simple four-sensor array discrimination of vapors from different classes can be readily achieved in most cases and discrimination of vapors within the same class is possible in many cases.

A new pattern recognition method, referred to as extended disjoint principal component analysis (EDPCR), has been developed for analyzing the multisensor array data. This method facilitates the identification and quantitation of the components of vapor mixtures and has several advantages over more conventional pattern recognition methods for this application.

Additional analyses have focused on the development of semi-empirical predictive response models based on the physical and chemical properties of the coatings and vapors. The models being examined are based on vapor boiling point, chromatographic specific retention volumes, solubility parameters, and solvatochromic indices. The slopes of the response vs. concentration curves for a set of test vapors are used to calculate experimental partition coefficients (K_E) , which represent the equilibrium ratio of the concentration of vapor in the coating to that in the air. These K_E values are then used in each of the four models to develop regression equations from which predicted K values (K_P) can be derived. The K_P values can then be used to predict SAW sensor responses for a given vapor/coating combination.

Linear correlations between K_E and K_P were obtained for all four models for the six coatings examined, with correlation coefficients (r2) ranging from 0.862-0.979. Best results were obtained with the more complex model based on solvatochromic indices, with K_P values falling within 60% of the K_E values for all of the vapors and coatings. However, this model is limited by a lack of solvatochromic indices for all vapors and coatings.

For the boiling point model, large errors in K_P were obtained for primary amines and alcohols on the less polar sensor coatings and for the non-polar hydrocarbon vapors on the more polar coatings. Notwithstanding these few outliers, the results obtained with this model are remarkably good given its simplicity. Most (>90%) of the K_P values were within a factor of two of the observed values for all coatings. Thus, reasonably good estimates of vapor selectivity are possible.

These results demonstrate the potential of these models for predicting the responses to untested target vapors, determining the importance of suspected interfering vapors, and choosing coating materials to optimize sensitivity and selectivity for a given vapor.

Publications

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Optical Remote Sensing and Computed Tomography in Industrial Hygiene

Lori A. Todd, Ph.D.
University of North Carolina, Chapel Hill
School of Public Health
Department of Environmental Sciences and Engineering
CB #7400 Rosenau Hall
Chapel Hill, North Carolina 27599-7400

Program Area: *Other Occupational Needs*
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Start & End Dates: *07/01/91 - 06/30/94*
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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

To date, computer algorithms are being developed to examine several geometries that require only a limited number of sources and detectors in the room. A computer simulation system is being developed to generate and test hundreds of test matrices.

Measurement Errors in Occupational Epidemiology

Donna Spiegelman, Sc.D.
Tufts University
School of Medicine
Department of Community Health
136 Harrison Avenue
Boston, Massachusetts 02111

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Grant Number: *1 K01 OH00106-01*
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Funding Level: *$53,872 ($53,872 Cum)*

Importance to Occupational Safety and Health

Nearly all occupational studies face problems measuring the exposure variable. Although other types of epidemiology are also faced with this problem, the necessity of retrospective exposure assessment in most cohort studies and the cost of detailed personal exposure sampling even in prospective and cross-sectional studies makes this a particularly difficult attribute of occupational safety and health research. It is quite possible that many occupational studies which have been interpreted as negative have in fact failed to detect important exposure-response relationships due to substantial exposure measurement error or misclassification. I propose to contribute to a resolution of these problems through the development of statistical methods to adjust point and interval estimates of

relative risk for bias due to measurement error. By illustrating these procedures with examples from important occupational data sets, it is hoped that the use of these methods of design and analysis will become standard practice in occupational epidemiology.

Objectives

1. To develop new measurement error methods applicable to retrospective cohort studies as typically found in occupational studies, which are simple to use and understand.
2. To develop new measurement error methods applicable to case-control studies as typically found in occupational epidemiology, which are simple to use and understand.
3. To develop new measurement error methods applicable to cross-sectional studies as typically found in occupational epidemiology, which are simple to use and understand.
4. To illustrate the use of these methods through the analysis of important occupational data sets, including
   a. the GM/UAW study of the relationship between respiratory and digestive cancer mortality and cumulative machining fluids exposure,
   b. the New Mexico uranium miners' study of the relationship between exposure to radon progeny and lung cancer mortality,
   c. the GM/UAW study of the relationship between acute respiratory effects and components of current machining fluids exposure, and
   d. the ACE study of the relationship 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

None to date.

Toxicological Effect of Vanadium on the Macrophage Response to Listeria Challenge

Cheng-i Wei, Ph.D.
University of Florida
Food Science and Human Nutrition Department
Gainesville, Florida 32611-0163

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Importance to Occupational Safety and Health

Vanadium-exposed workers were reported to be more susceptible to colds and other respiratory illnesses than non-exposed co-workers. It is suspected that vanadium affects host immunity and render the workers more susceptible to infectious agents. Using mice as a model, the information obtained in this study will contribute to the understanding of the underlying mechanisms involved in vanadium toxicity and its immunomodulating activity. Most of the reported immunotoxicity studies are primarily based on analyses of macrophage viability and phagocytic activity. Information obtained can be used to help establish a more accurate workplace exposure level of vanadium. In addition, the approaches employed in this study can serve as a basis for detailed mechanistic studies of the immunotoxicological effects of other heavy metals.

Objectives

The overall goal of this project is to determine if the decreased resistance of mice to *Listeria monocytogenes* due to vanadium treatment is through interference with peritoneal macrophage (PEM) ingestion and/or processing of the pathogen, or through inhibition of the T-cell mediated recruitment of bone marrow promonocytes to the

site of inflammation. The effects of vanadium treatment on the biochemical and structural aspects of mouse PEM as related to phagocytic and bactericidal functions will also be explored.

Methodology

Female $B_6C_3F_1$ mice weighing 18-20 g will be dosed IP every three days for 3 or 6 weeks with ammonium metavanadate (NH_4VO_3) solution in 0.1 M phosphate buffer (pH 7.2), NH_4Cl solution, or phosphate buffer. The doses of NH_4VO_3 will be 10.0, 5.0, or 2.5 mg/kg body weight. Three days after final challenge, the mice will be treated with *Listeria monocytogenes* for clearance studies, or sacrificed for the collection of PEM. Bacterial clearance from the peritoneal cavity, spleen, and liver will be performed in mice at 0, 2, 4, 8, 24, and 48 h post-infection with 3.3×10^3 *Listeria*.

The intracellular killing of *Listeria* by PEM will also be performed. PEM from *Listeria* challenged animals will be subjected to freeze-thawing in test tubes at 0, 15, 30, or 60 min for determination of intracellular bacterial numbers on trypticase soy agar.

To assay the activities of glucose-6-phosphate dehydrogenase, glutathione reductase, and glutathione peroxidase, PEM at 10^7/ml are subjected to freeze-thawing to prepare cytolysates for protein and enzyme assays. The release of β-galactosidase, lysozyme, hydrogen peroxide, leukotriene C, and interleukin-l will be determined with the appropriate methods. In addition, the superoxide anion production and the reduced and oxidized glutathione content in PEM will also be checked. The effects of vanadium treatment on macrophage cytoskeleton and macrophage membrane receptors for complement and IgG-F3 will be determined using the procedures of Solomon et al. (Cell 18:431, 1979).

Appropriate statistical analyses [analysis of variance (ANOVA), Duncan's comparison of means, and the Student's t-test] will be employed to determine the significance of vanadium treatment of the parameters investigated.

Significant Findings

Resident PEM from NH_4VO_3-treated mice and control groups (phosphate buffer and NH_4Cl) were subjected to flow cytometric analysis of $Fc_\gamma 2a$ and $Fc_\gamma 2b$ receptor expression, and photometric microassay to measure receptor mediated binding and phagocytosis of sheep red blood cells (SRBC). Similar $Fc_\gamma 2aR$ expression was observed with the phosphate buffer control and the 2.5V group. However, the NH_4Cl and 10V groups showed 21.7 and 17.2% lower mean fluorescence channel (MFC) values and 7.1 and 5.9% lower values in % fluorescence-positive cells than phosphate buffer control with respect to $Fc_\gamma 2a$ expression. For $Fc_\gamma 2bR$ expression, similar values for MFC and % fluorescent positive cells were obtained for the phosphate buffer, ammonium chloride and 2.5V groups. Only the 10V group showed a significant ($P < 0.05$) reduction in values of MFC (31.2 to 40.7%) and % fluorescence positive cells (15.1 to 15.7%) when compared to the other three groups.

No significant differences were observed among the four groups with respect to $Fc_\gamma 2aR$ mediated binding and phagocytosis of IgG-opsonized SRBC. However, significant decreases in $Fc_\gamma 2b$ mediated binding and phagocytosis were noticed for the 10V group when compared to the other three groups. The 10V group had a 20.1 and 35.7% lower binding and phagocytosis when compared to the phosphate buffer control, and 13.5 and 28.3% lower than the NH_4Cl group. There was no significant difference in $Fc_\gamma 2b$ mediated binding and phagocytosis in the 2.5V, the phosphate buffer and the NH_4Cl groups.

The reduction in $Fc_\gamma 2b$ expression and function could thus contribute toward the previously observed depression in phagocytosis, NADPH-oxidase and superoxide generation in vanadate treated animals.

Publications

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Owusu-Yaw J, Cohen MD, Fernando SY, Wei CI: An Assessment of the Genotoxicity of Vanadium. Toxicology Letters 50:327-336, 1990

Cohen MD, Fukayama MY, Wei CI: Immunotoxicological Studies of Ammonium Metavanadate in Mice. In: Biological Monitoring of Exposure to Metals, (eds. HK Dillon and MH Ho), John Wiley and Sons, Inc., pp. 127-144, 1990

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Wei CI, Cohen MD: *In Vivo* Vanadium Effect in the Clearance of *Listeria Monocytogenes* by Mouse Peritoneal Macrophages. Proc of the Sixth International Symposium on Molybdenum, Vanadium and Other Trace Elements held at Jena, German Democratic Republic, 1:86-92, July 3-6, 1989

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Wei CI, Cohen MD: Decreased Resistance to *Listeria Monocytogenes* in Mice Following Vanadium Exposure: Effects upon the Function of Macrophages. The Toxicologist 9:17, 1989 (Abstract #66)

Cohen MD, Wei CI: Effect of Ammonium Metavanadate Treatment upon Murine Peritoneal Macrophage Respiratory Burst-Related Biochemistry. FASEB J 2:A915, 1988 (Abstract #3607)

Cohen MD, Wei CI: Effects of Ammonium Metavanadate Treatment upon Macrophage Glutathione Redox Cycle Activity, Superoxide Production, and Intracellular Glutathione Status. J Leuko Biol 44:122-129, 1988

Sen AC, Cohen MD, Wei CI: Vanadium Inhibition of Glucose-6-phosphate Dehydrogenase and Glutathione Reductase *In Vitro*. FASEB J 2:A1819, 1988 (Abstract #8850)

TCD as a Screening Procedure for Exposures to Toxicants

Michael E. Drues
Iowa State University
Department of Biomedical Engineering
1146 Veterinary Medicine
Ames, Iowa 50011

Program Area: *Other Occupational Needs*
Grant Number: *1 R03 OH02932-01*
Start & End Dates: *09/30/91 – 09/29/93*
Funding Level: *$16,005 ($16,005 Cum)*

Importance to Occupational Safety and Health

Each year, thousands of new chemicals are developed and many may 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 biological 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.

Transcranial Doppler sonography (TCD) has been well established as a noninvasive and cost effective means of measuring cerebral blood flow in man. Deltamethrin, a commonly used pyrethroid insecticide, has been previously shown to increase CBF in rats as determined by other techniques. TCD would seem to have potential as a screening methodology for toxicants which may alter CBF, however, to date, it has not been used with animals nor has it been applied in the field of toxicology.

Objectives

The objective of this experiment is to evaluate the use of transcranial Doppler sonography as a screening procedure to detect occupational exposures to commonly used industrial and commercial chemical compounds. TCD provides a means of noninvasively measuring blood flow velocity in the brain. Since changes in cerebral blood flow (CBF) often occur prior to other clinical manifestations of chemically-induced toxicosis, a means of measuring changes in CBF could potentially be used as an early detection method for exposure to hazardous chemicals. If changes in

CBF can be detected by TCD prior to the occurrence of behavioral or other clinical signs, then interdictive measures could be initiated very early in exposure at a time when the effects of the toxicosis are either minimal or reversible.

Methodology

Fifteen greyhound dogs (>50 lbs.) will be suspended in a sling device to prevent movement without anaesthesia. These dogs will have chronic arterial and venous cannulas surgically implanted for the purpose of injectioning deltamethrin and recording mean arterial blood pressure (MAP). After healing, each dog will be placed into the sling to record normal TCD, EKG and MAP. Each dog will then be exposed to a low or high level of deltamethrin according to a Latin squares design. Results will be compared to determine the minimum level of deltamethrin required to elicit a significant change in cerebral blood flow, and determine if this exposure level is below the level where clinical or behavioral effects are observed.

Significant Findings

None to date.

Air Sampling Instruments Symposium

Beverly S. Cohen, Ph.D.
New York University
Medical Center
Lanza Labs
Longmeadow Road
Tuxedo, New York 10987

Program Area: *Other Occupational Needs*
Grant Number: *1 R13 OH02795-01*
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 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 be 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 would 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.

International Conference on Ethics, Health Policy, and Epidemiology

Barbara R. Visscher, M.D., Dr.P.H.
University of California, Los Angeles
School of Public Health
Department of Epidemiology
405 Hilgard Avenue
Los Angeles, California 90024-1772

Program Area: *Other Occupational Needs*
Grant Number: *1 R13 OH02825-01*
Start & End Dates: *08/01/90 - 07/31/91*
Funding Level: *$10,000 ($10,000 Cum)*

Importance to Occupational Safety and Health

This was an international conference on issues of ethics and health policy that arise in epidemiological practice and research. Some of these problems particularly relating to privacy, informed consent of subjects, and access to information sources have been described and discussed since the 1960s, but additional problems related to influence of sources of support on presentation of the results of studies, as well as critical review of methodologic issues, have also been recognized more recently. The International Epidemiological Association (IEA) has requested the development of a set of guidelines. This conference provided an opportunity for broad, open discussion of the various proposed guidelines which are being put forward. The two-and-a-half days prior to the Los Angeles International Scientific Meeting of the IEA on August 5-9, 1990, was an ideal opportunity to facilitate broad international participation in these discussions.

Funds provided partial support for one planning meeting, transportation, and subsistence for invited speakers and discussion leaders, and for publication of the proceedings.

Development of a Real Time, Continuous Isocyanates Monitor

David E. Hyatt, Ph.D.
ADA Technologies, Inc.
304 Inverness Way South, Suite 110
Englewood, Colorado 80112

Program Area: *Other Occupational Needs*
Grant Number: *1 R43 OH02913-01*
Start & End Dates: *09/30/91 - 03/31/92*
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

None to date.

Development of a Low-Cost Ethylene Oxide Detector

David E. Hyatt, Ph.D.
ADA Technologies, Inc.
304 Inverness Way South, Suite 110
Englewood, Colorado 80112

Program Area: *Other Occupational Needs*
Grant Number: *2 R44 OH02662-02A1*
Start & End Dates: *09/01/91 – 02/29/92*
Funding Level: *$396,315 ($443,222 Cum)*

Importance to Occupational Safety and Health

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

Objectives

The goal of this research and development program is to design, build, and test a prototype EtO monitor that is versatile enough to be used as an inexpensive hand-carried portable monitor or a wall-mounted area monitor. The prototype EtO monitor will operate continuously as a direct-reading instrument, employing a rugged solid state semiconductor sensor. A gas chromatography column will provide the specificity for EtO that is lacking in existing low-cost commercial real-time monitors. The prototype will be capable of providing an updated digital concentration readout once every minute and displaying an audible/visual alarm when the EtO concentration exceeds one of two preset levels. The final instrument design will incorporate low-cost components so that the

anticipated price of a commercial version will not exceed $4,000.

Methodology

The Phase II research program will expand on the work performed in Phase I. At the present time, a series of experiments are being performed to optimize the EtO sensor such that EtO sensitivity is maximized and interference sensitivity is minimized. SLX sensors have been set up in a test bed configuration in which the temperature and resistance of each sensor is monitored while the heater voltages of the sensors are varied. The test bed is enclosed in a temperature and humidity-controlled test chamber into which 4 ppm EtO, a simulated air mixture, or 1000 ppm of an interfering compound flows continuously. The experiments will determine the optimum heater voltage/temperature at which the EtO signal-to-noise ratio is maximized. These experiments will also provide data on the response of the sensor to various interferences.

Testing of chromatographic parameters has also begun. Various column materials have been obtained, and these will be evaluated for ability to elute EtO in one minute or less and for ability to resolve EtO from interferences. A single sensor operating at the optimum heater voltage identified in the previous task will be housed in an insulated metal block and the column outlet will be positioned as close to the sensor as possible. Different flow rates and column temperatures will be tested. When the proper column material and conditions have been identified, flow system parameters will be thoroughly evaluated, and a calibration procedure will be developed for the prototype instrument. Based on the results of these tasks, a prototype monitor will be assembled and tested in the laboratory. In addition, the instrument will be evaluated at various hospitals in the Denver area. Following the field testing, a preliminary design of a final instrument configuration will be proposed.

Significant Findings

The laboratory test plan to characterize the response of the semiconductor sensor element to ETO and to optimize this response was completed on schedule. This evaluation program defined the operating voltage and temperature of the sensor, its stability under these conditions, and the relative sensitivity of several specific detector models for ETO response.

Operating conditions for the chromatographic system employed to separate ETO and interferents were defined and the quantitative response of the column-sensor combination to ETO at concentrations of 0.1 to 10 ppm was demonstrated.

Carrier gas requirements for the chromatographic separation were defined and the development of appropriate gas purifier elements for the system was completed.

The prototype instrument was designed and constructed on the basis of the above laboratory tests and the operating data they provided. An on-board microcomputer for system operation, troubleshooting, and data logging was specified, acquired, and installed in the prototype.

Prototype instrument tests for ETO detection limit, baseline stability, and similar continuous operating performance are currently under way at ADA Technology laboratories. The plan to site the prototype instrument at a hospital site has been modified (due to liability considerations and to the desire to have a test environment in which intentional ETO leaks and interferent releases could be readily and safely achieved) and response tests will be conducted in an environmental chamber with complete atmosphere control capacity.

A major supplier of instrumentation to the ETO users marketplace has expressed interest in acquiring rights to the manufacture and sale of the ETO monitor and this Phase III development opportunity is being actively pursued at present.

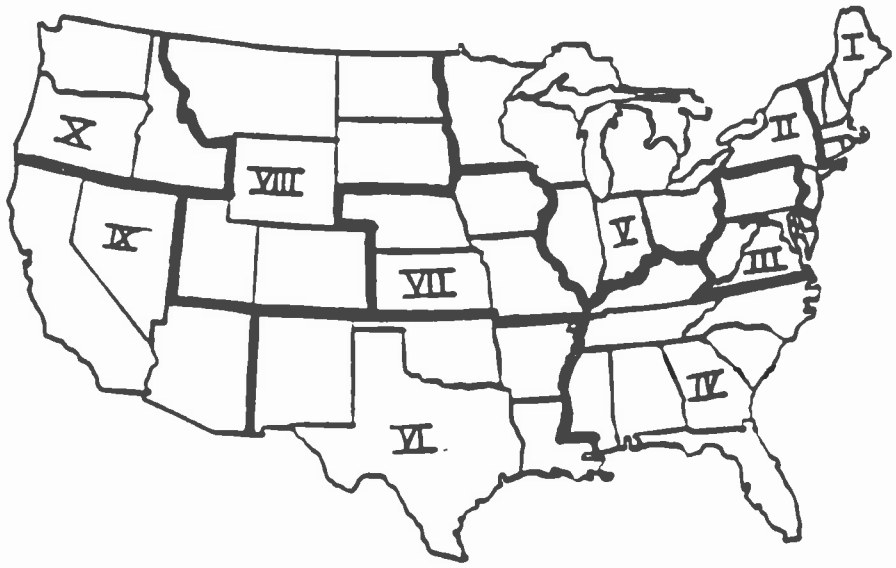
GRANTS ACTIVE DURING FY91

	COMPETING GRANTS		TOTAL GRANTS	
	No. of Awards	Amount of Awards	No. of Awards	Amount of Awards
Grants from FY91 Budget ($6.798M)				
Research Project Grants (R01)	15	$2,123,285	36	$5,548,659
Career Development Grants (K01)	5	$268,281	17	$851,194
Small Grants (R03)	4	$72,575	5	$94,836
Other Grants	5	$198,962	6	$302,909
Subtotal	29	$2,663,103	64	$6,797,598
Grants from FY90 Budget ($6.897M)				
Research Project Grants (R01)	3	$273,840	19	$2,075,035
Career Development Grants (K01)	0	$0	2	$64,752
Small Grants (R03)	3	$53,226	11	$228,786
Other Grants	3	$416,315	3	$416,315
Subtotal	9	$743,381	35	$2,784,888
Grants from FY89 Budget ($6.196M)				
Research Project Grants (R01)	5	$462,942	5	$462,942
Career Development Grants (K01)	2	$61,499	2	$61,499
Small Grants (R03)	3	$62,313	3	$62,313
Other Grants	1	$199,843	1	$199,843
Subtotal	11	$786,597	11	$786,597
Awards from all Years				
Research Project Grants	23	$2,860,067	60	$8,086,636
Career Development Grants	7	$329,780	21	$977,445
Small Grants	10	$188,114	19	$385,935
Other Grants	9	$815,120	10	$919,067
TOTAL	49	$4,193,081	110	$10,369,083

FY91 Grant Awards By Program Area

Program Area	Competing Grants		Total Grants		
	No. of Awards	Amount of Awards	No. of Awards	Amount of Awards	Amt. Per.
Occupational Lung Diseases	1	$116,147	8	$788,686	12%
Musculoskeletal Injuries	2	$103,194	5	$264,656	4%
Occupational Cancers	4	$173,190	9	$842,463	12%
Traumatic Injuries	2	$364,373	5	$718,957	11%
Cardiovascular Diseases	1	$54,000	1	$54,000	1%
Reproductive Disorders	1	$287,586	2	$552,289	8%
Neurotoxic Disorders	2	$395,203	3	$575,430	8%
Noise-Induced Hearing Loss	2	$281,464	4	$625,223	9%
Dermatologic Disorders	0	$0	1	$226,327	3%
Psychologic Disorders	2	$141,527	2	$141,527	2%
Control Techniques	3	$183,015	5	$322,577	5%
Respirator Research	1	$18,102	4	$266,652	4%
Other Occupational Needs	8	$545,302	15	$1,418,811	21%
TOTAL	29	$2,663,103	64	$6,797,598	100%

FY91 Grant Awards By Region And State
64 Grants Totalling $6,797,598



	No.	Amt.	(Per.)		No.	Amt.	(Per.)
Region I	11	$1,090,043	(16.0%)	Region II	10	$1,568,914	(23.1%)
Massachusetts	10	$1,004,833	(14.8%)	New Jersey	1	$103,947	(1.5%)
Vermont	1	$85,210	(1.2%)	New York	9	$1,464,967	(21.6%)
Region III	4	$543,339	(8.0%)	Region IV	7	$671,498	(9.9%)
Maryland	3	$394,585	(5.8%)	Alabama	1	$53,484	(0.8%)
Virginia	1	$148,754	(2.2%)	Georgia	1	$53,991	(0.8%)
				North Carolina	5	$564,023	(8.3%)
Region V	18	$1,451,931	(21.4%)	Region VI	3	$500,540	(7.4%)
Illinois	3	$171,342	(2.5%)	Oklahoma	2	$339,325	(5.0%)
Michigan	7	$670,113	(9.9%)	Texas	1	$161,215	(2.4%)
Minnesota	1	$18,102	(0.3%)				
Ohio	6	$539,179	(7.9%)				
Wisconsin	1	$53,195	(0.8%)				
Region VII	4	$394,842	(5.8%)	Region VIII	1	$48,868	(0.7%)
Iowa	3	$249,237	(3.7%)	Colorado	1	$48,868	(0.7%)
Missouri	1	$145,605	(2.1%)				
Region IX	5	$347,396	(5.1%)	Region X	1	$180,227	(2.6%)
California	5	$347,396	(5.1%)	Washington	1	$180,227	(2.6%)

Grant Number	Principal Investigator	Current Funding	Page
	Research Project Grants (R01)		
2 R01 OH00823-11A2	Mohamed B. Abou-Donia, Ph.D.	$197,019	92
5 R01 OH00835-12	William J. Swartz, Ph.D.	$59,118	85
3 R01 OH00978-09S1	James R. Trudell, Ph.D.	$292,338	140
5 R01 OH01122-09	Charles W. Kauffman, Ph.D.	$228,800	67
2 R01 OH01152-10A2	Donald Henderson, Ph.D.	$236,135	99
5 R01 OH01301-08	Klaus Willeke, Ph.D., CIH	$141,066	128
5 R01 OH01595-06	William C. Hinds, Sc.D.	$94,391	130
5 R01 OH01630-07	Edwin M. Uyeki, Ph.D.	$150,104	143
5 R01 OH02005-06	Philip I. Harber, M.D., M.P.H.	$76,720	131
2 R01 OH02067-08	G. Marie Swanson, Ph.D.	$75,317	53
3 R01 OH02091-05S1	James J. Nordlund, M.D.	$51,436	109
5 R01 OH02114-03	William W. Merrill, M.D.	$114,499	11
5 R01 OH02128-07	William W. Clark, Ph.D.	$145,605	100
5 R01 OH02148-07	Stephen F. Cleary, Ph.D.	$148,754	145
5 R01 OH02149-06	Ghulam A.S. Ansari, Ph.D.	$161,215	147
5 R01 OH02221-04	Stephen M. Rappaport, Ph.D.	$180,068	149
5 R01 OH02277-02	David Warshawsky, Ph.D.	$151,763	12
5 R01 OH02298-02	Kenneth D. Rosenman, M.D.	$34,068	14
5 R01 OH02317-07	Roger P. Hamernik, Ph.D.	$198,154	103
5 R01 OH02329-03	Richard P. Garrison, Ph.D.	$94,989	118
2 R01 OH02332-04	Edward H. Bergofsky, M.D.	$163,262	15
1 R01 OH02373-01A1	Walter F. Stewart, Ph.D.	$169,560	87
5 R01 OH02391-03	Nabih R. Asal, Ph.D.	$165,701	151
2 R01 OH02421-02A2	David C. Christiani, M.D.	$116,147	17
5 R01 OH02434-03	Mohamed M. Ayoub, Ph.D.	$41,963	37
5 R01 OH02437-02	David Leith, Sc.D.	$78,264	119
5 R01 OH02564-03	Arthur B. DuBois, M.D.	$141,912	134
2 R01 OH02571-04	Irvin Schonfeld, Ph.D.	$121,522	115
5 R01 OH02574-03	Ann H. Myers, Sc.D.	$213,159	38
3 R01 OH02591-02S1	Shihab Asfour, Ph.D.	$113,781	39
5 R01 OH02593-02	E. Neil Schachter, M.D.	$135,213	18
5 R01 OH02598-02	Allen A. Mitchell, M.D.	$264,703	88
5 R01 OH02601-03	Carol J. Garrett, Ph.D.	$173,274	68
5 R01 OH02611-03	Susan T. Bagley, Ph.D.	$92,833	54
1 R01 OH02614-01A1	Henry H. Emurian, Ph.D.	$26,630	82
7 R01 OH02618-02	Yehia Y. Hammad, D.Sc.	$77,608	20
5 R01 OH02621-02	William S. Marras, Ph.D.	$35,968	40
5 R01 OH02622-03	Regina M. Santella, Ph.D.	$226,327	111
5 R01 OH02629-02	Harvey Checkoway, Ph.D.	$120,617	94
3 R01 OH02647-01S2	George P. Hemstreet, III, M.D.	$173,624	56
5 R01 OH02651-02	James K. Hardy, Ph.D.	$39,242	152
5 R01 OH02663-03	Edward T. Zellers, Ph.D.	$86,573	153
5 R01 OH02666-02	Steven P. Levine, Ph.D.	$153,098	155
5 R01 OH02683-02	William Daniell, M.D., M.P.H.	$166,820	95
5 R01 OH02710-02	Michael R. Flynn, Sc.D.	$72,379	120
5 R01 OH02717-02	Philip J. Landrigan, M.D.	$61,155	70
5 R01 OH02719-02	Diana Echeverria, Ph.D.	$180,227	96

Career Development Grants (K01)

Small Grants (R03)

*U.S. GOVERNMENT PRINTING OFFICE: 1992-648-179/60016

Initiative Adopted by the
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September 1990