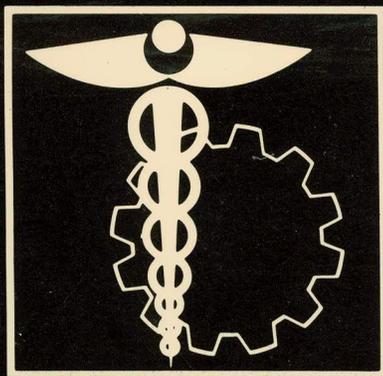


# NIOSH GRANTS

## RESEARCH and DEMONSTRATION PROJECTS



ANNUAL REPORT  
Fiscal Year 1989



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

**CDC**  
CENTERS FOR DISEASE CONTROL

# **NIOSH**

## **RESEARCH AND DEMONSTRATION GRANTS**

**FISCAL YEAR 1989**



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

June 1990

## **DISCLAIMER**

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

**DHHS (NIOSH) Publication No. 90-111**

## FOREWORD

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

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

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

Because the strengths of the extramural research program are the creativity and special resources that are available in the scientific community, we publish this report to stimulate submission of proposals for research of high quality on significant problems of occupational safety and health. We invite the interest of investigators in the biomedical sciences, engineering, and related disciplines. By including descriptions of all active grants during fiscal year 1989 (October 1, 1988 to September 30, 1989), 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 8,600 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: 513/533-8328



**ANNOUNCEMENT 923**

**Research and Demonstration Grants  
Relating to Occupational Safety and Health**

**Department of Health and Human Services  
Centers for Disease Control  
National Institute for Occupational Safety and Health**

**Application Receipt Dates:** New applications (February 1, June 1, October 1)

**Exceptions:** SERCA Grant applications, Small Grant applications, competing renewal applications, and revised applications (March 1, July 1, November 1).

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

Support in the form of individual (research, demonstration, and program) project grants will be awarded for annual budget periods, within a project period not to exceed five years.

**I. AUTHORITY**

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

**II. ELIGIBLE APPLICANTS**

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

**III. PROGRAM REQUIREMENTS**

**A. Research Project Grants**

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

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**B. Demonstration Grants**

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

**C. Special Emphasis Research Career Award (SERCA) Grants**

The SERCA grant is intended to: (1) provide opportunities for individuals with developing research interests to acquire experience and skill essential to the study of work-related hazards; (2) provide support for individuals to pursue a program of research in various disciplines; and (3) create a pool of highly qualified investigators with experience and skills 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 least at the doctoral level; (3) not be above the rank of associate professor; and (4) be citizens or noncitizen 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. Eligible applicants may reside at non-profit or for-profit organizations such as universities, colleges, research institutions, and other public and private organizations including State and local governments and small, minority, and/or woman-owned businesses.

This non-renewable award provides support for a three-year period for individuals engaged in full-time research and related activities, and may comprise direct costs of up to \$50,000 per year and additional indirect costs of 8 percent. 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). A minimum of 60 percent time must be committed to research, although full-time is desirable. A for-profit organization will be required to submit a certification as to its status as part of the application. Awards are made to institutions in the name of individual applicants.

A complete program announcement for the SERCA grant is available upon request (see "VIII. CONTACTS FOR FURTHER INFORMATION").

**D. Small Grants**

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

the person actually doing the work, the application should indicate who would be supervising the research. Small grant applications should be identified as such on the application form.

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

#### **E. Program Project Grants**

NIOSH will also accept applications for program project grants, but only after discussion with the individuals listed in this announcement. A program project grant is intended to support a broadly-based, multidisciplinary, often long-term research program which has a specific major objective or a basic theme. It should be directed toward a range of problems having a central research focus in contrast to the usually narrower thrust of the traditional research project. This type of grant generally involves the organized efforts of a group of established investigators, each of whom is conducting research projects designed to elucidate the various aspects or components of the overall objective.

#### **IV. FUNDING PRIORITIES**

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

1. Occupational lung diseases: asbestosis, byssinosis, silicosis, coal workers' pneumoconiosis, lung cancer, occupational asthma
2. Musculoskeletal injuries: disorders of the back, trunk, upper extremity, neck, lower extremity; traumatically induced Raynaud's phenomenon
3. Occupational cancers (other than lung): leukemia; mesothelioma; cancers of the bladder, nose and liver
4. Severe occupational traumatic injuries: amputations, fractures, eye loss, and lacerations
5. Cardiovascular diseases: hypertension, coronary artery disease, acute myocardial infarction
6. Disorders of reproduction: infertility, spontaneous abortion, teratogenesis
7. Neurotoxic disorders: peripheral neuropathy, toxic encephalitis, psychoses, extreme personality changes (exposure-related)
8. Noise-induced hearing loss

9. Dermatologic conditions: dermatoses, burns (scalding), chemical burns, contusions (abrasions)
10. Psychological disorders: neuroses, personality disorders, alcoholism, drug dependency
11. Control techniques: new technology performance evaluation, preconstruction review, equipment redesign, containment of hazards at the source, fundamental dust generation mechanisms, machine guarding/avoidance methods, explosion control, removal of emissions after generation, dispersion models, monitoring and warning techniques, technology transfer
12. Respirator research: new and innovative respiratory protective devices; techniques to predict performance; effectiveness of respirator programs; physiologic and ergonomic factors; medical surveillance strategies; psychological and motivational aspects; Effectiveness of sorbents and filters, including chemical and physical properties

## V. TECHNICAL REPORTING REQUIREMENTS

Performance reports on awarded grant projects are required annually as a part of the continuation application and a final report is due within ninety days of the end of the project period. The final performance report should be a technical report describing the original objectives of the study, the research methodology, the results, and the conclusions. It should include a list of publications resulting from the grant. Published (or submitted) research papers or theses may constitute an acceptable final report. The report should stand alone rather than citing the original application. Three copies of reprints of all publications prepared under the grant should accompany the report.

## VI. EVALUATION CRITERIA

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

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

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

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

- The review process will consider the applicant's scientific achievements, evidence of demonstrated commitment to a research career in occupational safety and health, and supportive nature of the

research environment (including letter(s) of reference from advisor(s) which should accompany the application).

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

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

A secondary review will also be conducted for programmatic importance. Factors considered in the secondary review will include:

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

## **VII. APPLICATION, SUBMISSION, AND DEADLINE**

Applications should be submitted on Form PHS-398 (revised October 1988) or PHS-5161-1 (revised March 1989) for State and local government applications and must include the drug-free workplace certification. Forms should be available from the institutional business offices or from:

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

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

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

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

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

The instructions in the Form PHS-398 packet should be followed concerning deadlines for either delivering or mailing the applications. The application should be sent or delivered using the mailing label in the Form PHS-398 packet.

The timetable for receiving and reviewing applications, and awarding grants, is given below.

<u>Application Deadline</u>	<u>Initial Review</u>	<u>Secondary Review</u>	<u>Expected Start Date</u>
February 1	June	September	December 1
June 1	October	January	April 1
October 1	February	May	August 1

**Exceptions:**

"Application Deadlines" are one month later for SERCA Grant applications, Small Grant applications, competing renewal applications, and revised applications.

"Secondary Reviews" and "Expected Start Dates" for SERCA Grant applications and Small Grant applications are one month earlier.

Awards will be made based on priority score ranking and emphasis area, as well as availability of funds.

**VIII. CONTACTS FOR FURTHER INFORMATION:**

**For Programmatic Information Contact:**

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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.

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

## Pulmonary Toxicity of the Semiconductor, Gallium Arsenide

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Program Area: *Occupational Lung Diseases*

Grant Number: 5 R01 OH02076-03

Start & End Dates: 11/01/84 - 10/31/88

Funding Level: \$131,079 (\$372,512 Cum)

### Importance to Occupational Safety and Health

Gallium arsenide is a semiconductor used in the electronics industry and there is potential worker exposure via inhalation during the manufacturing process. The pulmonary response to gallium arsenide and to its potential dissolution products has been investigated in previous years in this grant and been found to involve an inflammatory response. If the actual toxic species from GaAs which caused the lung response were determined, a better understanding of the potential long-term effects should be possible. One of the products of GaAs hydrolysis would be arsine (AsH<sub>3</sub>) and, if formed, this compound would result in substantial systemic toxicity.

### Objectives

The objective of this work was to determine the conditions necessary to form arsine from gallium arsenide and to evaluate its potential formation *in vivo*. The general objective is to determine if arsine may be the toxic species formed in the lung from GaAs.

### Methodology

Electronic grade GaAs (99.999%) was ground into a powder and treated with 2-3 ml of the test solutions in a Thunberg tube. Any gaseous reaction products formed were swept out by a stream of nitrogen gas (5 l/min) into the hydrogen-nitrogen diffusion flame of an atomic absorption spectrophotometer. Alternatively, the gas stream was bubbled through an absorption vessel containing 5 ml of a 0.3% solution of silver diethyldithiocarbamate in chloroform containing 1% morpholine. If arsine was obtained as a reaction

product, the solution in the absorption tube turned a red color. This was quantified in a visible spectrophotometer. The presence of arsine dissolved in the reaction mixture was also determined by the colorimetric procedure. The identification of the gas as arsine was confirmed by mass spectrometry.

### Significant Findings

Arsine gas was only formed when GaAs was treated with concentrated hydrochloric acid, and this reaction was enhanced in the absence of air. No arsine was formed with water, mixtures of chloride salt solutions, perchloric acid, sulfuric acid, nitric acid, ascorbic acid, citric acid, acetic acid, or ammonia.

It was interesting that the formation of arsine from GaAs and concentrated hydrochloric acid was inhibited by the presence of many metal ions. Salts of aluminum, iron (III), cadmium, tin (II and IV) and As (III) prevented the formation of arsine. Zinc metal and zinc salts did not prevent the arsine formation.

It was concluded that arsine would not be formed *in vivo* and that it is not the agent which causes the GaAs-induced pulmonary toxicity. Subsequent work on another project demonstrated the formation of As (III) on the GaAs crystal surface when the GaAs was exposed to Gamble's solution, a synthetic lung fluid. Thus, As (III) is released during GaAs dissolution and, along with GaAs particles, is probably responsible for the lung toxicity of GaAs.

Previous work showed that 100 mg/kg GaAs caused pulmonary inflammation equivalent to 200 mg/kg silica within 2 weeks after a single dose, and the effects were dose-dependent for GaAs. By 6 months, the GaAs did not develop the nodular fibrosis like silica, and most parameters returned to near normal. Microscopy indicated increased alveolar wall thickness and foamy macrophages at 6 months. The 2.5 mg/kg GaAs dose did not cause the lung changes.

### Publications

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Rosner MH, Carter DE: Pulmonary Changes Following Intratracheal Instillation of Gallium Arsenide and Arsenic and Gallium Oxides in Hamsters and Rats. *Toxicol* 8:148, 1988 (Abstract)

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Snider BJ, Zhang J, Carter DE: Biochemical and Histological Pulmonary Effects of Gallium Arsenide Compared to Silica after an Intratracheal Dose. *Toxicol* 7:198, 1987 (Abstract)

Bellamy WT, Carter DE: Urinary Porphyrins as a Measure of Arsenic Exposure in the Rat. *Toxicol* 6:261, 1986 (Abstract)

Mitchell RD, Snider BJ, Carter DE: Indicators of Systemic Toxicity in Three Animal Species Following Arsenic III Exposure. *Toxicol* 6:262, 1986 (Abstract)

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## Epithelial Surface Proteins: Markers of Cancer Risk

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Program Area: *Occupational Lung Diseases*  
Grant Number: *5 R01 OH02114-03*  
Start & End Dates: *01/01/86 - 12/31/89*  
Funding Level: *\$135,956 (\$429,736 Cum)*

### Importance to Occupational Safety and Health

Workers who are exposed to the fibrous silicate asbestos experience an increase in several diseases of the lower respiratory tract. The two most frequent and dramatic are a predisposition to bronchogenic carcinoma and a chronic inflammatory and fibrotic reaction in lung parenchyma termed "asbestosis". Both diseases are found with increased frequency in those with an occupational asbestos exposure. Cigarette smoking increases the risk of cancer and may also increase the risk of asbestosis in these workers. We assess metaplasia as an index of cancer risk with two probes (histologic and biochemical) and study fibrosis with standard lung

function and mechanisms of injury revealed by cells and proteins recovered from bronchoalveolar lavage. Our goal is to find early markers or predictors of these diseases. Such markers might allow therapy at an early stage prior to development of irreversible pathology.

### Objectives

There were two independent objectives in these studies. Metaplasia was assessed in this population by performing bronchial biopsies and quantifying the degree of metaplasia in the biopsies by a qualitative 4 point scale. In addition to 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.

### Methodology

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

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

## Significant Findings

*Characterization of the population:* The asbestos worker study population was comprised of subjects with positive chest x-rays. Approximately 50% of the population had pleural plaques while the remainder had parenchymal opacities. All had at one time been cigarette smokers; however, 60% had stopped smoking from 1 to 32 years prior to bronchoalveolar lavage. Each subject had significant asbestos exposure with an average of  $14.5 \pm 2.4$  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. There was no evidence that smoking history or asbestos exposure *per se* was predictive of metaplasia. Secondly, 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 detectable in 54% of the asbestos workers. However, there is no relation between keratins in BAL fluid and the presence of metaplasia detectable by bronchial biopsy.

*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 ( $8.6 \pm 2 \times 10^6$  neutrophils per BAL) than those without fibrogenesis ( $1.5 \pm 0.5 \times 10^6$ ). BAL neutrophil number correlated inversely with the diffusion capacity as a percent of predicted ( $R = -0.56$ ). Significantly, those with evidence of lung injury had a greater loss of diffusion capacity over time compared to those with relatively normal lungs.

## Publications

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

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## Environmental Toxicity of Isocyanates

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

### Importance to Occupational Safety and Health

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

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

### Objectives

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

### Methodology

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

chemistry methods. *In vitro* labeled targets are being investigated in a similar manner after complete characterization of the specificity of reaction under defined conditions.

### Significant Findings

Exposures have been performed using radioactively labeled TDI, HDI, and MIC. Analysis of the uptake and distribution of the label shows a linear dose dependent increase in plasma radioactivity during exposure which continues to a maximum uptake approximately one hour post-exposure. In all cases, independent of isocyanate concentration, the level of radioactivity decreased over the following 72 hrs to a nanomolar concentration of label which persisted up to two weeks post-exposure. A linear relationship was observed between the rate of initial uptake of radioactivity into the blood and concentration of isocyanate during a one-hour exposure. Independent of the isocyanate used, this relationship holds for the correlation of uptake rate and ppm hours. Thus for the isocyanates, the uptake is dependent primarily on the total accumulated dose, not simply on concentration. Analysis of urine, bile, and tissues showed that the uptake and clearance patterns for the three isocyanates are similar, and parallel the pattern found for blood. For all three isocyanates, the primary targets were the airway tissues.

Examinations of nose, trachea, and lung by light microscopy revealed a dose dependent progression of tissue injury for all three isocyanates. The immediate response was characterized by intraepithelial edema, cell destruction, and complete desquamation of the epithelium in some areas. Autoradiography showed the radioactivity to be localized on and beneath the airway epithelium. At low concentration, evidence of injury prior to both cell loss or deposition of radioactivity was observed. SDS PAGE and immuno-localization analysis of airway tissues showed laminin to be specifically labeled by all three isocyanates.

Biochemical analyses were performed to characterize exposure-related, dose-dependent labeled, and unlabeled molecules in the blood and airway tissues. Separation of blood from TDI and HDI exposed animals showed label only in the plasma fraction, whereas both plasma and cell fractions were found labeled in blood from MIC exposed animals. In the latter case, intracellular hemoglobin was found to be labeled, and the amount of label followed a linear dose dependence. Detailed analysis of the plasma fraction by HPLC and SDS PAGE showed a single 68K-labeled protein for TDI and HDI exposures and

multiple-labeled proteins for MIC. Examination of gel filtration HPLC profiles of lung extracts from exposures to all three isocyanates revealed a unique, dose-dependent, HPLC peak which did not contain radioactivity. Preliminary analysis of the material shows it to be approximately 2000 molecular weight with an absorbance maximum at 254 nm.

#### Publications

Kennedy AL, Stock MF, Alarie Y, Brown WE: Uptake and Clearance of  $^{14}\text{C}$  During and Following Inhalation Exposure to [ $^{14}\text{C}$ ] Toluene Diisocyanate. *Toxicol Appl Pharmacol* 100:280-292, 1989

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

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

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

## Mechanism and Treatment of Phosgene Poisoning

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Program Area: *Occupational Lung Diseases*  
Grant Number: 5 R01 OH02264-05  
Start & End Dates: 08/01/84 - 09/29/90  
Funding Level: \$153,757 (\$662,108 Cum)

### Importance to Occupational Safety and Health

As man relies more and more on synthetic chemistry for new industrial and consumer products, the occupational risk of exposure to inhaled toxic gases increases in the chemicals industry. However, because synthetic plants for production of these chemicals are often located near major metropolitan areas, and because toxic gases are routinely transported in concentrated liquid form by rail and truck through urban centers, transportation and storage accidents can now threaten whole communities that once felt comfortably remote from chemical plants.

### Objectives

As a model for toxic gas inhalation, we chose phosgene, because it is commercially important, can be obtained from suppliers in reliable concentrations, is highly reactive, and produces intense alveolar injury. Using phosgene inhalation as a model, we studied lung injury from toxic gas inhalation with the following objectives in mind: (1) characterize the acute alterations in vascular and airway physiology occurring after phosgene exposure; (2) determine whether agents elevating cyclic AMP protect from phosgene lung injury, and if so, their mechanism of protection; (3) define the role of leukotrienes and other arachidonic acid metabolites in lung injury from phosgene; (4) study the contribution of leukocytes to producing or magnifying lung injury from phosgene; and (5) determine if neutral metalloendopeptidase, a lung epithelial enzyme important in metabolism of tachykinins, can serve as a marker of lung injury from inhaled toxic gases.

### Methodology

For the majority of our studies, we exposed rabbits to 2,000 ppm-min phosgene (200 ppm for 10 min) and perfused their lungs in a recirculating manner with Krebs-Henseleit buffer either immediately or 4 hours after phosgene exposure. Pulmonary arterial and tracheal pressures were continuously monitored, and lung edema formation was assessed by cumulative lung weight gain. Microvascular permeability was assessed by determining rate of lung weight gain at increased outflow pressures, and by following passage of  $I^{125}$ -albumin from the vascular space into lung water and lung lavage fluid. Levels of cyclooxygenase and 5-lipoxygenase products of arachidonic acid metabolism in effluent lung perfusate were measured using radioimmunoassays. Recently, we have developed a rat model of phosgene lung injury in collaboration with the U.S. EPA in Research Triangle Park, NC. Injury in this model is assessed at 2 and 24 hours after phosgene exposure by measuring concentration of protein and thiobarbituric acid reactive products in lung lavage fluid. Activity of neutral metalloendopeptidase in lavage fluid was measured using an HPLC assay based on cleavage of a synthetic substrate.

### Significant Findings

Phosgene caused marked pulmonary edema and a striking fall in dynamic lung compliance in rabbits. Lung edema was caused by a marked increase in lung microvascular permeability, because phosgene did not increase pulmonary arterial pressure but produced a striking rise in lung microvascular permeability to  $I^{125}$ -albumin and a marked increase in rate of lung weight gain at elevated outflow pressures. In perfused rabbit lungs, oxidants and other injurious agents cause pulmonary vasoconstriction by stimulating lung production of thromboxane. The failure of phosgene to increase pulmonary arterial pressure was because phosgene did not stimulate lung generation to thromboxane. However, the ability of phosgene-exposed lung to produce thromboxane from infused arachidonic acid remained intact. Agents capable of increasing cyclic AMP provided marked protection from phosgene lung injury. The beta agonists terbutaline and isoproterenol, the phosphodiesterase inhibitor aminophylline, and the cyclic AMP analog dibutyryl cyclic AMP all strikingly protected against lung weight gain from phosgene and prevented the phosgene-induced increase in lung microvascular permeability to  $I^{125}$ -albumin. We demonstrated that the cyclooxygenase inhibitor ibuprofen provided marked protection from phosgene lung injury, even

when given after gas exposure. The mechanism of protection, however, appeared to have nothing to do with inhibiting the lung cyclooxygenase metabolism. Rather, we found that ibuprofen can function as an iron chelator and hydroxyl radical scavenger both *in vivo* and *in vitro*. This represents a new mechanism of action for this drug and may partially explain its benefit in other inflammatory disorders. Lung effluent levels of leukotriene  $C_4$  were markedly elevated after phosgene exposure. Also, phosgene lung injury was strikingly reduced by the leukotriene synthesis inhibitors methylprednisolone and 5- $\alpha$ ,8-,11-,14-eicosatetraenoic acid, or by the leukotriene receptor blockers FPL 55712 and LY171883. Thus, phosgene lung injury appears to be mediated at least in part by stimulation of lung 5-lipoxygenase metabolism. Studies in our rat model indicate that leukocytes play a prominent role in magnifying phosgene lung injury. Depleting leukocytes with cyclophosphamide or inhibiting leukocyte influx into lung with colchicine substantially reduced phosgene lung injury in rats. In contrast to what we had anticipated, lavage fluid activity of neutral metalloendopeptidase is significantly reduced in rats after phosgene exposure. Thus, bronchoconstriction from phosgene may be in part mediated by impaired metabolism of tachykinins in airways.

### Publications

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

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## Influence of Particulates on Occupational Lung Disease

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Program Area: *Occupational Lung Diseases*  
Grant Number: *1 R01 OH02277-01A2*  
Start & End Dates: *09/30/89 - 09/29/92*  
Funding Level: *\$166,651 (\$166,651 Cum)*

### Importance to Occupational Safety and Health

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

### Objectives

The long-term objective of this research is to investigate the role that AMs play in the particulate-dependent response of the lung to BaP via a mechanism involving BaP metabolism. Although the mechanism of cocarcinogenic action is unknown, several investigators have implicated BaP metabolism. An important biological response to inhaled particulates is ingestion by AMs and clearance from the lung. Since these cells have the capacity to metabolize BaP, it is possible that altered BaP metabolism leading to an enhanced carcinogenic potential occurs in the AM following phagocytosis of silica particulates and adsorbed BaP.

### Methodology

Male Syrian Golden hamsters are known to be susceptible to the formation of lung tumors by BaP-coated particulates. AMs will be lavaged from male Syrian hamsters and cultured in 100 x 20 mm tissue culture dishes. At the end of 24 hours, which will allow adequate time for cultures to stabilize, BaP or BaP adsorbed onto different forms of silica, and cytochrome C will be added to each dish. At the end of each incubation period, the culture medium will be removed and an aliquot will be analyzed for the amount of cytochrome C reduced. The remainder of the medium will be extracted with ethyl acetate. The ethyl acetate extract will be analyzed by HPLC to quantitate metabolites and parent compound. The aqueous layer will be analyzed for the presence of conjugate. The AMs will be removed and an aliquot will be analyzed for viability by exclusion staining. The remaining cells will be analyzed as described above. Additional studies will be conducted to compare the extent of binding to DNA and protein to the release of metabolites from the cell. The DNA and total protein will be isolated by the phenol extraction method. The extent of binding will be determined by liquid scintillation spectrometry.

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

### Significant Findings

Work is in progress on particle sizing of BaP coated forms of silica. Since the grant was not funded until September 30, 1989, there are no significant findings to report during FY89.

### **Pilot Project to Assess Mortality Among Former Chromium Smelter Workers**

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Program Area: *Occupational Lung Diseases*  
Grant Number: *1 R01 OH02298-01A2*  
Start & End Dates: *07/01/89 - 06/30/91*  
Funding Level: *\$95,886 (\$95,886 Cum)*

#### **Importance to Occupational Safety and Health**

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

#### **Objectives**

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

#### **Methodology**

A cohort mortality study of workers from five chromate producing plants will be performed. Former workers will be contacted regarding their willingness to participate in a medical screening.

#### **Significant Findings**

The grant was funded for only three months this fiscal year. Computerization of cohort records is in progress.

### **Effect of Particle Load on Alveolar Clearance**

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Grant Number: *5 R01 OH02332-03*  
Start & End Dates: *01/01/87 - 03/31/90*  
Funding Level: *\$142,347 (\$406,616 Cum)*

#### **Importance to Occupational Safety and Health**

Airborne particles of an infectious, industrial, or environmental nature are constantly inhaled and must be cleared by lung defense mechanisms. These mechanisms include mucociliary clearance from the tracheobronchial tree and cell mediated clearance from alveoli. Recent evidence in our laboratory and others indicate that at high particulate lung burdens, cell mediated lung clearance is altered. The current overload hypothesis states that cell function and movement may become impaired when cells ingest particles equal to 25% of their volume.

The purpose of this study is to examine the routes of particle clearance from deposition sites in an effort to quantify the lung clearance mechanisms under normal and load conditions in an animal model close anatomically and physiologically to man. Detection of alterations in clearance rate and/or route with increased particle load may discern the initiating event and particle dose leading to disease. Additionally, identification of particle sequestration sites pinpoint areas where excessive accumulation of even bland particles may potentiate their inflammatory capacity by increasing lung residence time. Further, cell-particle interactions at high particle burdens impair cell function (phagocytosis and activation) may lead to inflammatory reactions through the release of inflammatory mediators, thereby reducing alveolar clearance. Investigations along these lines should reveal factors which lead to failure of the clearance system responsible for eliminating particles from the alveolar surface which may consequently aggravate their inflammatory and fibrogenic potential in the lung parenchyma.

### Objectives

1. Quantitate the sites of particle deposition within the tracheobronchial tree and alveoli after a reproducible inhalation technique.
2. Quantitate the rate and routes of normal (low load) particle clearance from the lung.
3. Quantitate alterations in rate and route by increasing particle burdens to the lung.
3. Characterize particle-macrophage interactions of exiting and resident macrophages.
4. Identify sites of particle sequestration from increased particle burden.

### Methodology

Our approach will permit us to determine, in a quantitative manner, the clearance routes of two sized particles (0.5 and 3 CMD) after deposition in the alveolar portion of the lung. The methods of assessing routes of particle clearance include: (1) gamma camera imaging (for overall pattern and rate of clearance) *in vivo* and *in vitro*, after sacrifice and extirpation of the lung; (2) surveillance of routes of exits via: (a) whole lung lavage for the content of macrophage-related and unrelated particles, (b) creation of tracheal stomae for collection and analysis of mucus for its particles and macrophages, (c) lymph nodes for particle accumulation, (d) metabolism study for routes of clearance; and (3) light and electron microscopic corroboration of original sites of deposition and particle sequestration during the course of clearance from extirpated lung tissue.

Cellular function and activation under increasing particle load will be evaluated by the following: (1) cytotoxic capacity against actinomycin D-treated L929 cells determined by crystal violet staining for cell density; (2) procoagulant and fibrinolytic activity as measured by binding of human plasminogen to membrane and detection by flow cytometry through monoclonal antibodies; and by an extrinsic pathway coagulation assay employing enzyme linked human fibrinogen; (3) release of oxygen metabolites as assayed by reduction of dyes such as dichlorofluores to its fluorescent oxidized product and supraoxide release by iodotetrazolium violet; (4) phagocytizing capacity by exposing collected macrophages with *in vivo* internalized particles to a second set of fluorescent particles of the same or different sizes *in vitro*; and (5) Fe $\gamma$  receptor levels of macrophages as determined by binding monomeric sheep IgG or immune complexes during incubation and subsequent reaction with rhodamine labeled anti-sheep IgG. These tagged cells are fixed and subjected to dual wavelength flow cytometric analysis.

### Significant Findings

1. Sites of particle deposition have been characterized.
2. Equivalent tracheobronchial clearance is complete in 45 hours.
3. Alveolar clearance has a half life of 30 days, which is prolonged under high particle loads.
4. Particle sequestration sites have been located in peribronchial lymphoid tissue.
5. Particle-cell ratios, in regard to particles/cell and number of egressing cells/unit time, change as load increases.

### Publications

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## Lung Disease in Chinese Textile Workers

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

### Importance to Occupational Safety and Health

This study is a longitudinal follow-up of cotton textile workers in Shanghai, China. The relevance of the knowledge gained from this work includes: the relative contributions of cotton dust and gram negative bacterial endotoxins in producing acute and chronic respiratory disease; the rate of annual decline in lung function after exposure to cotton dust; and the importance of acute, cross-shift change in FEV<sub>1</sub> in predicting longitudinal loss of lung function. Determination of exposure-response for gram negative bacterial endotoxins is important not only for textile workers, but also for thousands of workers exposed to other organic dusts and environments rich in endotoxin.

### Objectives

Briefly stated, the project objectives have been:

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

subsequent development of respiratory symptoms and loss of FEV<sub>1</sub>.

### Methodology

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

### Significant Findings

Eighty-seven percent of the original cohort was identified at the time of the 5-year survey. There were no significant differences in symptoms or baseline pulmonary function between those retested and those lost to follow-up. Cotton textile workers reported an excess of both acute and chronic symptoms as compared with silk workers, after adjustments for smoking. Dyspnea, a chronic symptom, was the symptom of highest prevalence at follow-up. The majority (63%) of byssinotics at the time of first survey reported dyspnea 2+ five years later. In a logistic regression model, endotoxin level better predicted dyspnea prevalence than dust level.

Cotton textile workers had an accelerated 5-year decline in pre-shift FEV<sub>1</sub> as contrasted with silk workers, and the effect of cotton exposure appeared additive with smoking. In an autoregressive model, FEV<sub>1</sub> change was strongly predicted by exposure to cotton after adjustments for age, sex, height, and smoking. A cross-shift change in FEV<sub>1</sub> at initial survey was also strongly predictive of 5-year decline in FEV<sub>1</sub> after adjusting for age and smoking.

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## Airway Hyperreponsiveness Due to Cotton Bract Exposure

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Grant Number: *1 R01 OH02593-01A1*  
Start & End Dates: *09/01/89 - 08/31/91*  
Funding Level: *\$131,942 (\$131,942 Cum)*

### Importance to Occupational Safety and Health

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

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.

### Objectives

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

### Methodology

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

Objective 1: The working hypothesis is that smokers have an asymptomatic, low-level airway inflammation that makes them more susceptible to increases in CBE-induced airway responsiveness. 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 working hypothesis is that repeated exposures to CBE results in progressively greater inflammatory changes in the airway that will manifest themselves by airway hyperresponsiveness. 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

At this writing, no data are available for reporting.

### Publications

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## A Rational Method for Sampling Airborne Fibrogenic Dust

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 Grant Number: *1 R01 OH02618-01*  
 Start & End Dates: *12/01/88 - 03/30/91*  
 Funding Level: *\$91,953 (\$91,953 Cum)*

### Importance to Occupational Safety and Health

Current sampling instruments of respirable dust (RD) may over estimate 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  $\mu\text{m}$  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<sup>3</sup> aerosol sampling chamber through a TSI Inc. Kr-85 particle neutralizer model 3054. The aerosol is thoroughly mixed within 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 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<sup>3</sup> 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 Perkin-Elmer Lambda 1 UV/VIS spectrophotometer is utilized for all UMB mass determinations. 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.

### Significant Findings

To verify proper air flow patterns, the performance of the new aerosol sampling chamber was evaluated qualitatively using smoke tubes and quantitatively using filters positioned at different locations within the sampling compartment. The results indicate that the air flow patterns and aerosol concentrations are even throughout the chamber with a CV of 6.3%. The generation system produced mono-dispersed aerosols with geometric standard deviations <1.2. Calibration of the 6 impactors indicated that their effective cut-off diameters are 1.61, 1.94, 2.32, 2.7, 3.12 and 3.56  $\mu\text{m}$ . Performance of the 10 mm cyclone was also evaluated at air flow rates of 0.5, 0.75, 1, 1.5, 2 and 3 lpm for both the nylon and aluminum versions. The penetration of the aluminum cyclone was consistently higher than that of the nylon version.

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## Silicosis and Pulmonary Cancer

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Program Area: *Occupational Lung Diseases*  
 Grant Number: *1 R01 OH02726-01*  
 Start & End Dates: *06/01/89 - 05/31/91*  
 Funding Level: *\$144,447 (\$144,447 Cum)*

### Importance to Occupational Safety and Health

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

### Objectives

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

### Methodology

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

## Significant Findings

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

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## Pharmacomechanical Hyperresponsiveness in Ozone-Induced Airway Injury

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 Grant Number: *7 K01 OH00060-01*  
 Start & End Dates: *03/01/88 - 02/28/92*  
 Funding Level: *\$32,400 (\$32,400 Cum)*

### Importance to Occupational Safety and Health

Our current research aims are to determine *in vivo* and *in vitro* mechanics which increase airway muscarinic responsiveness. This has and will continue to be done in subjects with bronchial hyperreactivity, the increased airway irritability which characterizes asthma and ozone-induced lung injury. What we have learned from our previous studies of airway structure and function in this disorder suggests that injury to normal lung constituents results in the elaboration of factors leading to cholinergic neuromuscular hyperresponsiveness. Among the many potential cell types that could influence bronchomotor tone are cells of the respiratory mucosa which may affect airway muscle both pre- and post-synaptically. From our work it appears that airway muscle responsiveness in acute, ozone-induced bronchial hyperreactivity is increased, and that this hyperresponsiveness is linked to more than one

noncyclooxygenase, mucosa-derived factor in the guinea pig. Thus, we speculate that the hyperreactivity developing acutely after ozone exposure may be due to mucosa-derived factors which increase the responsiveness of airway muscle.

### Objectives

Increased bronchial irritability (bronchial hyperreactivity) is a characteristic feature of asthma, and understanding its pathogenesis may provide new insights for better treatment. In guinea pigs with acute O<sub>3</sub>-induced airway injury, we have found that cholinergic hyperreactivity may be related to a lipooxygenase product, possibly leukotriene, elaboration. Our recent studies have suggested that intralobar bronchial and tracheal muscle, from ozone-exposed airways, is hyperresponsive to ACh and KCl *in vitro*. We now aim to (1) confirm whether or not the *in vitro* muscarinic responsiveness of certain airway generations is increased in animals with ozone-induced bronchial hyperreactivity, and (2) study whether electromechanical or pharmacomechanical properties of smooth muscle cells from certain airway generations differ in animals with ozone-induced bronchial hyperreactivity.

### Methodology

To accomplish Aim 1, we will compare the effect of ozone- and sham-exposure *in vivo* on (a) smooth muscle preparations from different airway generations and on (b) airway muscle muscarinic responsiveness to endogenously released (via electrical field stimulation (EFS)) versus exogenous ACh. If ozone exposure augments EFS responsiveness, its possible pre-synaptic effects will be more directly assessed by measuring <sup>3</sup>H-ACh release from intramural cholinergic nerve terminals of airways. To further satisfy Aim 2, potential post-synaptic, electromechanical effects will be assessed by the simultaneous measurement of muscle cell membrane potential and force development in different airway generations upon cholinergic stimulation after ozone exposure. To investigate possible pharmacomechanical effects of ozone of muscarinic contraction that may be extracellular Ca<sup>++</sup>-independent, muscle preparations will be studied in zero Ca<sup>++</sup>.La<sup>+++</sup> buffer.

### Significant Findings

Airway mucosal cells are particularly vulnerable to the damage caused by ozone inhalation. The possible effects of respiratory mucosal oxidant injury on its metabolic functions, including its neutral

endopeptidase (NEP) activity, are considerable. To investigate whether ozone-induced respiratory injury in guinea pigs results in the inactivation of airway NEP and an increased reactivity to substance P, we assessed the influence on airway substance P reactivity of phosphoramidon (PHA), an antagonist of NEP. Reactivity before and after ozone (3 ppm, 2h) or air exposure was determined by measuring specific airway resistance in intact, unanesthetized, spontaneously breathing animals in response to increasing doses of intravenous substance P boluses. We found that PHA increased substance P reactivity in the air-exposed animals, but it had no effect in the ozone-exposed group. Furthermore, we found that inhalation of a normal saline aerosol containing partially purified NEP isolated from guinea pig kidney and characterized by HPLC, reversed the ozone-induced increase in substance P reactivity to preozone levels in all animals tested. Inhalation of heat inactivated NEP aerosol had no such effect. Our data indicate that ozone exposure decreases airway NEP activity and increases substance P reactivity which can be reversed by aerosolized NEP.

We have investigated whether O<sub>3</sub> exposure of guinea pigs augments the contractile response of their airway smooth muscle (ASM) *in vitro* in the presence of 10 μM indomethacin. Mucosa-intact tracheal rings from ozone-exposed and control animals were stimulated by increasing doses of ACh, KCl, or substance P (SP) in the presence or absence of 1 μM phosphoramidon, an inhibitor of metalloendopeptidase which may be abundant in airway mucosal cells. Guinea pigs were studied in pairs. One of each pair was exposed to room air while the other was exposed to 3ppm O<sub>3</sub> for 2 h and became hyperreactive. Muscarinic reactivity was determined by measuring specific airway resistance (SRaw) in response to increasing doses of aerosolized ACh administered before and 30 min after exposure. Those animals exposed to O<sub>3</sub> showed substantial muscarinic hyperreactivity: isometric force generation *in vitro* (at optimal length) was measured upon stimulation by cumulative doses of the agonists and force (in gm/cm<sup>2</sup>) was calculated after determining ASM cross-sectional area. The smooth muscle of mucosa-intact airways from guinea pigs with ozone-induced bronchial hyperreactivity proved to be hyperresponsive *in vitro* to substance P and ACh, but not to KCl. Pretreatment with phosphoramidon abolished this increased substance P responsiveness, but had no effect on muscarinic hyperresponsiveness after ozone exposure. Furthermore, substance P responsiveness was not augmented on ozone-exposed airways in which the mucosa had been removed prior to testing *in vitro*. Likewise,

muscarinic hyperresponsiveness was not present in ozone-exposed airways without mucosa. Our data suggest that smooth muscle responsiveness is increased in guinea pigs with ozone-induced bronchial hyperreactivity, and that this hyperresponsiveness is linked to more than one noncyclooxygenase, mucosa-derived factors.

Airway mucosal cells may be a rich source of metalloendopeptidase. We have isolated cytosolic and membrane fractions from homogenates of bovine tracheal mucosa to identify the presence of metalloendopeptidase activity in airway mucosal cells. We then directly assessed the effect on this activity of hypochlorous acid (HOCl), a product of myeloperoxidase-catalyzed oxidation of chloride, which may be generated during oxidant airway injury. We have concluded that metalloendopeptidase activity is present in bovine airway mucosal cells, and this enzyme activity is markedly inhibited by the oxidant HOCl.

#### Publications

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

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Richards IS, Ousterhout J, Sperelakis N, Murlas CG: Cyclic-AMP Suppresses Ca<sup>++</sup>-Dependent Electrical Activity of Airway Smooth Muscle Induced by TEA. *J Appl Physiol* 62:175-179, 1987

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### Inhaled Toxic Agents: An Evaluation of Dose

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Grant Number: *5 K01 OH00067-03*

Start & End Dates: *07/01/87 - 06/30/90*

Funding Level: *\$29,956 (\$94,756 Cum)*

#### Importance to Occupational Safety and Health

The characterization of the risk upon exposure to an inhaled agent must consider the dose-response relationship between the agent and the respiratory tract. The evaluation of the dose-response relationship must, however, follow 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 characterization of the exposure-dose relationship during respiratory exposures is to be evaluated by a deterministic mathematical model of the mass transport process of respiratory gas absorption. The model will include 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 will also be evaluated both from a theoretical viewpoint and empirical analysis.

### Methodology

To assess target tissue dose, we are developing a mathematical model, based on the principles of mass transport, to predict the mass flux as a function of distance into the respiratory system. The mathematical model will be generalized to the respiratory absorption of gases 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 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 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 currently 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 ( $\bar{x}=4.05 \pm .21$  mm,  $n=6$ ) was significantly greater than those of living subjects ( $\bar{x}=2.88 \pm .76$  mm,  $n=24$ ). These differences suggest postmortem shrinkage or distortion of the turbinate. In further evaluation of airway resistance 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.

We have also attained the solution to the mathematical model of pollutant gas absorption. We have shown a nearly 40% reduction in gas penetration to the central airways for each ten fold increase in the Henry's Law constant. We have also determined that morphometry, both upper and lower airway dimensions, influences regional dose. However, to date, we have not yet altered the upper airway compartment to reflect our new morphometric analysis. Consequently, the variables in the model are perimeter and cross-sectional area. Increases in perimeter and cross-sectional area associated with decongestion were predicted to reduce the fractional penetration by 15% compared to the congested state. In the lung, central airway dose was found to increase with the lowering of lung volume. This increase does not persist into the periphery and thereby suggests that increased central airway responsiveness may not indicate increased dose to the lung periphery. The variability in responsiveness for similar exposure regimes has become the focus of the present research.

In conjunction with the modeling of respiratory gas absorption as a function of morphometric variability, we have been developing a fluorescence spectroscopy technique to evaluate the mass transport coefficients within the upper airway. We are testing the technique by measuring the mass transport coefficients in straight tubes for which the coefficients are known. We are determining the transport coefficients in tubes from 2-14 cm in length at intervals of 2 cm. In distinguishing the coefficients at these intervals, we are proving that

we have the sensitivity to measure the coefficients within the nasal cavity where mass transport coefficients are much higher. Once the system is calibrated, we will perform measures of the coefficients in human nasal cavity models. To do so, we are developing a method to transfer the 3-D image reconstruction of the CT scans of living subjects to a CAD-CAMM system. This work will represent the first generation of a model based on the upper airway morphometry *in vivo*.

#### Publications

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

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### The Immunopathogenesis of Occupational Diseases Due to Reactive Chemicals

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Start & End Dates: 09/30/88 - 09/29/91  
Funding Level: \$32,400 (\$64,800 Cum)

#### Importance to Occupational Safety and Health

Reactive small molecular weight chemicals are recognized as important causes of occupational asthma (OA) and reactive airways disease. Occupational asthma is associated with exposure to various types of diisocyanate chemicals including toluene diisocyanate (TDI), diphenylmethane diisocyanate (MDI) and hexamethylene diisocyanate (HDI) in approximately 5% of exposed workers. Evaluations of workers have demonstrated that only 10% of symptomatic workers develop specific IgE responses to relevant diisocyanate human serum albumin (HSA) antigens (1). As a result, other nonimmunologic mechanisms have been postulated. A prior study showed that most workers with TDI asthma exhibit *in vitro* cellular immune responses after stimulation with specific TDI-HSA antigens

suggesting that cellular immunity may play a significant pathogenic role (2). Much less is understood regarding the pathogenesis of occupational hypersensitivity syndromes related to exposure to reactive metal such as chromium. Evidence obtained in our laboratory suggested that specific cellular immune responses could mediate such responses to reactive metals (3). Thus, it was postulated that specific *in vivo* cellular responses to diisocyanates and chromium compounds 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 the *in vivo* laboratory methods that measure cellular responses to specific occupational antigens would allow development of assays which could identify symptomatic workers or workers at potential risk for development of occupational immunologic diseases. These methods could be more sensitive than currently available *in vitro* immunoassays that measure specific IgG and IgE responses to these chemical antigens.

#### Objectives

The first objective of this proposal is to define whether specific cell mediated immune responses are detectable in workers with occupational asthma. This question was to be studied in workers identified with OA associated with exposure to MDI and a separate group with OA or anaphylactoid reactions associated with exposure to chromium compounds.

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

#### Methodology

The populations to be studied are comprised of: (1) 20 workers with exposure to MDI of whom 10 have been diagnosed with OA and 10 with no occupational disease; (2) 5 workers with clinical diagnosis of OA or hypersensitivity responses associated with exposure to chrome or chromic acid. Parallel studies were planned on 5 asymptomatic control subjects with no previous exposure to either chromium or diisocyanates. Relevant test antigens

are prepared by coupling MDI, HDI, and TDI to HSA and  $\text{Na}_2\text{CrO}_4$  to HSA followed by complete chemical characterization of resultant conjugates. The chromium population is evaluated by delayed skin patch testing to  $\text{Na}_2\text{CrO}_4$  and the MDI population by intracutaneous and epicutaneous testing to MDI-HSA, TDI-HSA, and HDI-HSA. To detect specific humoral immune responses, serum samples will be assayed for specific IgG (ELISA) and specific IgE (RAST) to MDI-HSA and  $\text{Na}_2\text{CrO}_4$ -HSA antigens. A panel of *in vitro* cellular assays are performed on all subjects including: (1) antigen-induced lymphocyte blast transformation; (2) the direct leukocyte inhibitory factor (LIF assay) in response to HSA conjugates of TDI, MDI, and HDI; and finally (3) an assay for histamine releasing factor (HRF) derived from supernatants of 18-hour lymphocyte cell cultures after stimulation with relevant occupational antigens.

### Significant Findings

Of 3 subjects with known clinical sensitivity to diisocyanates confirmed by direct bronchial or cutaneous challenge studies, HRF activity was detected in response to MDI-HSA and TDI-HSA in one and to TDI-HSA alone in another subject. No significant HRF activity has been detected in 4 other recently exposed workers without documented bronchial sensitivity to diisocyanates.

A significant LIF response expressed as percent inhibition of migration ( $>2$  times mean of nonexposed controls;  $N=10$ ) was detected in 4 diisocyanate exposed workers which included the 3 workers with known clinical sensitivity. Only one diisocyanate exposed worker had specific IgG to MDI-HSA and serum specific IgE tests to diisocyanate antigens were negative in all subjects.

Of 2 chromium sensitive subjects that have been evaluated, HRF activity has been identified in lymphocyte supernatants of one subject in response to  $\text{Na}_2\text{CrO}_4$ -HSA (500  $\mu\text{g}/\text{ml}$ ); the second subject with OA exhibited a positive delayed patch test, LIF activity, and the presence of HRF in response to  $\text{Na}_2\text{CrO}_4$ .

Thus, these early findings suggest that specific *in vitro* cellular immune responses can be detected in workers with occupational hypersensitivity syndrome associated with exposure to reactive agents in the workplace.

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## Immune Responsiveness in Chlorine Exposed Rats

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

### Importance to Occupational Safety and Health

Long-term effects on respiratory health of sub-lethal irritant gas exposures are not fully understood. Irritants may induce or exacerbate airway obstruction in some individuals or may increase susceptibility to sensitization to common environmental antigens. Industrial vapors, including chlorine, may cause similar problems, but their effects have not been well studied. Chlorine is an important chemical in over 50 industries, including paper processing and water sanitation. In 1975, NIOSH estimated that 15,000 individuals had potential occupational exposure to this agent. Thus, it is important to know the effects of exposure. If our findings indicate substantial risk of enhanced susceptibility to antigen sensitization, this would provide guidance in the design of studies or surveillance programs for exposed working populations. Inclusion of appropriate tests for clinical follow-up of exposed individuals would also be warranted.

### Objectives

The objective of this grant is to develop an animal model to evaluate the effects of acute, high-level chlorine gas exposure on functional aspects of the immune system of BALB/c mice.

### Methodology

Mice are exposed for 1 hour to chlorine gas. Briefly, whole body exposures take place in a stainless steel and glass horizontal laminar flow exposure chamber, which has been modified for use with irritant gas. Animals can be observed at all times during the exposure period. As a safety precaution for laboratory personnel, the chlorine gas generation system is turned off after termination of

exposures, and air flow in the chamber is maintained until a continuous monitor indicates that the gas concentration in the chamber is one-half of the OSHA permissible exposure limit. A self-contained breathing apparatus is immediately available for all personnel.

Immediately, 3 hours, or 1, 7, 30, or 60 days post-chlorine exposure, mice are exposed, by nose only, to bovine serum albumin (BSA). Antigen exposures are performed for 30 minutes, 5 consecutive days. Animals are then rested for 10 days. Test sera and bronchoalveolar lavage fluid (BALF) are obtained at sacrifice. BALF is retrieved using *in situ* lavage of both lungs; retrievable cells are isolated by centrifugation and used in phenotypic analysis. For that analysis, lymphoid cells are quantitated using monoclonal antibodies and flow cytometry. For antibody studies, BALF is concentrated approximately 15 times by Amicon ultrafiltration. Antigen (BSA) specific IgG, IgA, and IgM are quantitated using an enzyme linked immunosorbent assay (ELISA). This is a standard assay, except that goat sera has been substituted for BSA in all appropriate solutions. Specific IgE is quantitated using a passive cutaneous anaphylaxis test in rats. Also at sacrifice, spleens are excised from animals, and a single cell preparation is used for phenotypic analysis and lymphocyte transformation. Lymphocyte transformation, with both antigen and mitogen, is performed using standard assays, except that cells are treated with mercaptoethanol. Data from test animals are compared with those obtained from non-chlorine exposed controls.

### Significant Findings

Animals exposed to chlorine and immediately to aerosolized BSA appeared to have higher specific IgG levels in sera than did breathing air-exposed animals. No differences were seen in IgA or IgM levels. Changes in lymphoid cell populations decreased over time in both chlorine and breathing air-exposed animals, suggesting that the changes occur as a result of aging.

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

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

### Importance to Occupational Safety and Health

Exposure to respirable coal mine dust has been strictly controlled in the United States since the enactment of the Mine Safety and Health Act in 1969. To accurately study the relationship between exposures to coal dust and respiratory diseases in this "post-MSHA" period, accurate estimates of exposure are required. This study will provide quantitative estimates of the exposure-disease relationship at low levels of exposure to coal mine dust and allow an evaluation of the effectiveness of current exposure levels in the U.S.

### Objectives

1. To quantitatively estimate the exposure levels of respirable coal mine dust for a cohort of underground miners.
2. To assess the relationship of exposure to coal mine dust to pulmonary function status.

### Methodology

A cohort of underground coal miners has been followed for respiratory health by NIOSH since about 1971. A sub-cohort of these miners who started working in 1970 or later will be selected for an exposure-response analysis.

Estimates of mean exposure to respirable dust will be made within categories defined by mine, occupation, and year. The data used to estimate exposure are derived from MSHA compliance programs. The various potential biases present in the data set are first evaluated and then controlled when possible. Exposures within work categories with little or no data are estimated using a series of decreasingly specific stratifications. The exposure estimates are then matched to the cohort's work

histories and measures of cumulative exposure derived.

Exposure-response analyses will be conducted by modeling the effect of cumulative exposure and potential confounders including smoking history on the pulmonary function status of the miners.

#### Significant Findings

Various potential biases have been identified in the exposure data and, where possible, methods to control for the biases have been adopted. The method used to estimate exposure levels has successfully estimated means with reasonably small standard errors. These means were matched to the cohort's work history and a mean cumulative exposure of 15 mg/m<sup>3</sup>-yrs was obtained.

#### Publications

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

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

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### Immuno-Epidemiology of Crab-Induced Occupational Asthma

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Program Area: *Occupational Lung Diseases*

Grant Number: *1 R03 OH02654-01*

Start & End Dates: *04/01/89 - 03/31/91*

Funding Level: *\$21,675 (\$21,675 Cum)*

#### Importance to Occupational Safety and Health

This research should be useful in determining the prevalence of various general health conditions among women (predominately 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 crabs 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, four 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 eighth month of a two-year timeline. Approximately 205 current employees (175 from the cohort enumeration and 30 who recently joined or returned to the workforce) from 9 processing plants participated in the prevalence study (about an 85% participation rate). Only approximately 50 former workers were successfully recruited, however. An initial sample of 150 was drawn out of 650 enumerated former workers, and letters of invitation sent. Approximately 50 letters were returned as undeliverable and 25 participants completed the interview and skin tests. An additional 100 letters were sent, resulting in another 25 participants, including those recruited with additional followup from the initial group. Data from both study phases have been edited, coded, and are being entered for computer data analysis. Because of the difficulty recruiting former workers to the study, special emphasis will be necessary to determine whether former workers differ from non-participant.

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## Development of a Model for Prediction of Optimal Lifting Motion

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Program Area: *Musculoskeletal Injuries*  
Grant Number: *5 R01 OH02434-02*  
Start & End Dates: *01/01/88 - 12/31/90*  
Funding Level: *\$78,857 (\$158,965 Cum)*

### Importance to Occupational Safety and Health

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

### Objectives

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

### Methodology

The focus of this study is on joint behavior during manual lifting motions. The magnitude of the torque of each joint is predicted for each time increment of the lifting motion. Model constraints are the limitations imposed by the three types of given information and characteristics of the human body, of the task, and of the work place. The algorithm of the simulation is to construct a path, which may not be initially feasible, and work toward optimality (and if necessary, feasibility) with each iteration. This method proceeds as follows:

1. A Picture Generator Function (PGF) is selected, the PGF "base" is defined as a straight line from the initial posture to the final posture;
2. Parameters for the PGF are randomly selected;
3. A set of motion paths are generated using the PGF. The program sifts the combination of these paths that can satisfy (a) physical constraints, (b) kinematic constraint, (c) kinetic constraints.
4. If there is more than one feasible path, the path with the "best" objective function value is selected. If no path is feasible, a path is chosen at random.
5. If the change in objective function value is less than a specified criteria, or the prescribed execution time is exceeded, the program is terminated; otherwise go to step 2 using the current path as the "base" for the PGF.

Within the given constraints and the input information, the program simulates the following output: (1) it demonstrates the feasible body positions that allow the person to reach the box to be lifted; (2) for each feasible body position, it determines the acceleration and change of acceleration within the kinematic capacity; (3) after simulating all of the possible kinematic combinations of different stages, the model predicts the segment forces that the subject will be able to exert and provides a description as well as a graphical display of the body posture. The resultant motion of these body postures is based on obtaining the smallest resultant value for the objective function. This objective function value serves as a motion selection rule.

### Significant Findings

Effort has been mainly focused on four approaches. First, the effects of learning on the performance of simple lifting tasks were examined. One hundred twenty lifts were selected at approximately evenly spaced intervals from the

laboratory lift data collected. The selected lifts were examined two ways. The biomechanical measure used as the objective function for the model was calculated and plotted as a function of the lift replication number (i.e., number of lifts performed). The results indicated a small rise in objective function value from lift number 1 to lift number 20, followed by a decreasing profile in the value as the lift number increased to number 120. From this we conclude that after an initial familiarization period, the lifting performance exhibited the classical effect of learning. The trajectories of the angular displacement for all five joints were also examined to determine whether the angular displacement curves approaching the model-generated, optimal lift curves as the number of lifts increased. We found that, in general, this was not the case. We found that the lift time tended to decrease as a direct cause of the number of lifts, making this type of comparison difficult. Due to the lack of close agreement between model generated motion patterns and those obtained from the laboratory experiment, several new biochemical performance measures were considered as candidate objective functions. The biomechanical measures examined were:

1. The time integral of sum of absolute values of the torque acting on the articulation joints during the performance of the task.
2. The time integral of the sum of the absolute value of mechanical power acting on the articulation joints during the performance of the task.
3. The sum of the moment arm for the box and all body segments about the fulcrum of the ankle.

It was found that all three new objective functions produced similar motion patterns. Effort was then directed to fine tune the model to perform more in line with the results of the laboratory lifting data.

Because of the significant deviation in the motion patterns from one single subject performing the same lifting tasks under the same environment, this research tends to simulate a set of feasible movements rather than an optimal lifting pattern only.

#### Publications

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

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## Back Injuries in Municipal Employees

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Program Area: *Musculoskeletal Injuries*  
Grant Number: *5 R01 OH02574-02*  
Start & End Dates: *09/30/88 - 09/29/91*  
Funding Level: *\$204,202 (\$382,397 Cum)*

### Importance to Occupational Safety and Health

Low back injuries account for more absence from work than any other disease. Municipal employees are a high-risk group. In order to design interventions to reduce injuries, it is necessary to identify the risk factors associated with the injuries. A multidisciplinary 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 among employees in the four departments with the highest rates of low-back injury: Transportation, Recreation and Parks, Education, and Public Works.

### Objectives

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

### Methodology

Data will be collected from injury reports, medical records, personnel records, site visits, and by means of in-person interviews of cases and controls. Cases will have sustained low back injury while at work; back pain must be acute in onset and

result in restricted activity or lost work time. One control will be individually matched to each case on the basis of department, job, gender, and presence at work on the day the case was injured. A second control will be drawn from workers in all departments who have the same job classification. Personal interviews of cases and controls will be conducted within ten days of injury. In addition, site visits will be made to reconstruct the case's activity at the time of injury among those who report lifting, pulling, pushing, or pressing tasks.

Data for the ergonomic analysis of selected tasks will be analyzed by the consulting ergonomists using appropriate analytic techniques. In addition to being part of the multivariate analysis, these data will also be compared to the site visit data.

Data will be analyzed according to univariate and multivariate methods for matched pairs. A conditional logistic regression model will also be utilized. The findings of this study should form the basis for planning effective interventions to reduce occupationally-related lower back injuries.

#### Significant Findings

The pilot study has been completed and a debriefing session is planned for early December, 1989. The study will proceed after any necessary modifications are made.

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## Ergonomic Injury Control in High Frequency Lifting Tasks

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Program Area: *Musculoskeletal Injuries*  
Grant Number: *5 R01 OH02591-02*  
Start & End Dates: *09/30/88 - 09/29/90*  
Funding Level: *\$95,632 (\$187,707 Cum)*

#### Importance to Occupational Safety and Health

This study is unique in that industrial workers, rather than student volunteers, are being 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 frequency of lifting. This information could be applied in industrial settings to reduce musculoskeletal injury and improve work performance.

#### Objectives

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

#### Methodology

The methodology proposed in this research is a modified psychophysical approach where the subject is given control of the lifting duration rather than the amount of load lifted. Human lifting capabilities will be 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). Three heights of lift will be studied, namely, floor to table, table to shoulder, and shoulder to reach. The duration of each experimental session, referred to in the proposed research as endurance time, will be treated as a response variable.

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

Endurance time in this study is 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 will be set at 8 hours.

Each subject will be given 10 minutes of rest for every 50 minutes of work and 1 hour for lunch after the fourth hour of work. The ratings of perceived exertion (leg, back, arm, shoulder, hand, overall body, and local) will be recorded for every 50 minutes of work and upon termination of the experimental session.

Each subject will be asked to lift a compact box (38 x 38 x 25 cm) using a freestyle lifting technique in an environmentally controlled laboratory. The box will be lowered automatically using a mechanical device.

### Significant Findings

During the first year of the project, the studies conducted concentrated on data collection of endurance time and physiological responses of subjects involved in high repetition lifting tasks (8, 12, 16 lifts/minute) for a wide range of loads (5, 10, 15 kg) from floor to table height and from table to shoulder height. A total of 360 treatments have already been completed in the past 12 months. The results obtained, thus far, indicate that both the load and the frequency of lift have a significant effect on endurance time, heart rate, and oxygen consumption. These results were mainly based on data collected on subjects that are 20 - 49 years of age, and lifting boxes from floor to table height. It is interesting to note that the mean endurance time values in the present study were much higher than the mean endurance time values obtained in the pilot study conducted at the University of Miami in 1987 and which was referred to in the original proposal. These differences could be attributed to the fact that in the present study industrial workers participated as subjects in the experiments while in the pilot study, the subjects were student volunteers.

The results obtained from this project at the end of the second year will help in filling the gaps found in the manual materials handling literature for the determination of human lifting capabilities for continuous high frequency lifting tasks.

## Quantitative Measures of Wrist Motions

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Program Area: *Musculoskeletal Injuries*  
Grant Number: *1 R01 OH02621-01*  
Start & End Dates: *01/01/89 - 12/31/90*  
Funding Level: *\$33,248 (\$33,248 Cum)*

### Importance to Occupational Safety and Health

Cumulative trauma disorders (CTDs) are disorders of the soft tissues (most frequently 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 the industrialized world is unknown, but epidemiological data reveal that CTDs are a growing problem. Overall, CTDs are the second most frequently reported category of occupational illness after skin disease. Because of the frequency and impact of CTDs on worker health, NIOSH has designated musculoskeletal injuries (including CTDs) as one of the ten leading work-related diseases and injuries (Tanaka et al., 1988). During the five-year period from 1980 to 1984, data from the Ohio Industrial Commission show that the wrist was affected in almost half of all CTD claims.

Wrist posture and repetition have often been cited qualitative as risk factors associated with CTDs. However, researchers do not know to what degree wrist angle and repetition places a worker at risk. What is needed are specific quantitative measures of wrist angle and repetition that place the worker at risk. These quantitative measures could be used as a foundation of a work practices guideline whose purpose would be to inform industry engineers and managers on how they could reduce hand/wrist CTDs.

## 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 which quantitatively relates wrist motions to the risk of CTDs in this area. The primary objective of this research is to find the correlation between kinematics of wrist motion and the risk of a specific occupationally induced CTD, carpal tunnel syndrome (CTS). Specifically, wrist angle, velocity, and acceleration in both the radial/ulnar and flexion/extension planes of workers in industry will be correlated with degree of CTS risk. Pronation and supination will also be documented. The results of this correlational analysis will be used to determine which specific wrist motion characteristics are associated with high 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.

## Methodology

This research will be implemented in three steps.

1. Development of Quantitative Methods - A wrist monitor that records wrist motion in both the radial/ulnar and flexion/extension planes were developed in our lab. In the worst case scenario (maximum exertions), the monitor records wrist angle, velocity, and acceleration within 3.5%, 8.5%, and 10.5% accuracy, respectively. This monitor is easy to put on subjects and does not require individual calibration.
2. Industrial Documentation - We will take the monitor out into industries that have highly repetitive hand/wrist tasks and collect wrist motion data from workers while they are performing their jobs. We will choose jobs in which workers have low and high levels of CTS incidence. The incidence will be determined from OSHA 200 log data and medical records. Twenty-four subjects (12 in low risk group, 12 in high risk group) will participate in this study. The potential subject pool will be open to active workers of all genders, ages, experience, and history of CTDs.
3. Analysis and Interpretation - The data collected in step 2 will be analyzed. The wrist motion kinematic variables will be correlated with level of CTS risk.

## Significant Findings

Step 1 in the Methodology section has been completed. The wrist monitor and software have already been developed and tested, and it is feasible to measure wrist angle, velocity, and acceleration.

We are currently working on step 2 in the Methodology section.

## Publications

Schoenmarklin RW, Marras WS: An Investigation into the Effects of Angled Hammers and Hammering Orientation. Part I: Wrist Motion and Hammering Performance. Human Factors, in press, 1989

Schoenmarklin RW, Marras WS: An Investigation into the Effects of Angled Hammers and Hammering Orientation. Part II: Muscle Fatigue and Subjective Impressions. Human Factors, in press, 1989

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## Biomechanical Assessment of Work Tasks and Musculature

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Grant Number: *1 R03 OH02684-01*  
Start & End Dates: *09/28/89 - 09/27/90*  
Funding Level: *\$21,750 (\$21,750 Cum)*

## Importance to Occupational Safety and Health

Workers engaged in manual material handling tasks are predisposed to "overexertion type" low back injuries. The lumbar extensor muscle group is most often at risk of injury and is considered the weak link in the worker's biomechanical system. Typically, treatments of these injuries address the immediate symptoms, ignoring the mechanisms causing the injury and subsequent re-injury. Assessment of the worker's task mechanics and strength capacity would identify biomechanical flaws as well as strength requirements for specific tasks.

The lumbar extensor strength required for specific tasks (predicted through three-dimensional

dynamic kinetic analysis), in addition to evaluation of isolated lumbar extensor strength, would enable correlation of specific tasks to a worker's biomechanical and strength capabilities. This correlation would allow appropriate placement of workers in tasks suitable to their innate strength and ultimately reduce the frequency of low back injuries. In addition, this correlation would allow quantitative rehabilitation assessment following injury, which would provide the ability to monitor the worker's progress, thus facilitating recovery and return to work.

### Objectives

This study will compare an individual's lumbar extensor strength to the strength demands of a specific work task in order to provide a more accurate functional assessment. This quantitative assessment will allow assignment of workers (injured, rehabilitating, and normal-uninjured) to tasks appropriate for their strength, a particularly important point when evaluating injured workers currently undergoing rehabilitation. This pilot study is limited to the evaluation of normal individuals.

Three specific aims have been identified for the project:

1. Dynamic three-dimensional evaluation of specific work tasks for normal individuals and subsequent calculation of lumbar extensor force requirements.
2. Comparison of lumbar extensor force requirements for specific work tasks with the actual strength of the isolated lumbar extensors for normal individuals using the MedX lower back muscle testing machine (MedX, Inc., Ocala, FL).
3. Evaluation of physiological processes (electromyographic data and oxygen consumption) to assess fatigue and energy expenditure during task performance.

### Methodology

In order to accomplish the project objectives, the methodology is separated into two phases, software development and data acquisition.

#### 1. Software Development

Using 3-D data acquired with the Motion Analysis System, reflective markers attached to body landmarks will be located in the work space during task performance. Following optimization and definition of body segments, Unix-based software

will be developed to calculate the following three-dimensional information:

- a. body position from spatial coordinates of landmarks
- b. angular position, velocity, and acceleration of body segments
- c. linear acceleration of body segments
- d. inertial moments and forces on body segments
- e. reactive moments and forces at spinal articulates (external forces)
- f. equilibrium forces of the lumbar extensor (internal forces)

#### 2. Normal data acquisition

Twenty normal subjects will be evaluated performing simple work tasks. Reflective markers will be applied to the body landmarks and eight Sensormedics surface electromyographic electrodes will be placed bilaterally on the lumbar extensor at L5 and L1 as well as the gluteus maximus and hamstrings. Oxygen consumption will also be monitored during task performance by the Waters Oxygen analyzer.

The subject will be positioned in the work space with four CCD video cameras strategically positioned so that each body marker is viewed in two cameras at all times during the task performance. Two work tasks will be evaluated. The first task involves squatting, lifting a box from the floor, twisting, and placing the box on a table to the left of the worker. The second task involves lifting a loaded box from a table on the worker's left, twisting to the right, and placing the box on a table at the worker's right. Each task will be repeated for 100 cycles with data acquired at six regular intervals throughout 100 cycles: after 10 cycles, 30 cycles, 50 cycles, 70 cycles, 90 cycles, and 100 cycles. The motion data will then be processed to reveal the forces and moments on the spine and the deterioration of motion with time. The required strength of the lumbar extensor muscles will then be estimated from the kinetic analysis.

These normal individuals will also be tested on the MedX machine in order to determine the maximum isometric strength of their isolated lumbar extensor. The subjects will then be placed under constant isotonic tension throughout multiple cycles of flexion and extension for ten minutes and tested again for maximum isometric strength following fatigue.

The subject's force production measured by the MedX will then be correlated with the required strength to perform the specific work task determined through the kinetic analyses.

### Significant Findings

Grant was only recently awarded.

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## A Longitudinal Study of Musculoskeletal Disorders

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Program Area: *Musculoskeletal Injuries*  
Grant Number: *1 R03 OH02689-01*  
Start & End Dates: *08/15/89 - 08/14/91*  
Funding Level: *\$26,100 (\$26,100 Cum)*

### Importance to Occupational Safety and Health

Musculoskeletal disorders are a widespread cause of impairment and disability in labor-intensive occupations. Limited epidemiologic evidence has linked upper extremity soft tissue disorders (UESTDs) such as carpal tunnel syndrome (CTS) and tendinitis to occupational ergonomic stressors. The objective of the proposed research is to contribute to the improvement in epidemiologic study of musculoskeletal disorders, through information derived from a longitudinal study of workers occupationally exposed to ergonomic stressors.

The vast majority of the epidemiologic research conducted on work-related musculoskeletal disease to date has been cross-sectional. It is therefore particularly important to attempt to estimate the magnitude of the "healthy worker survivor effect" and the resulting underestimation of work-related increases in risk. Also, prospective data are needed on the conditions under which episodic pain becomes persistent or remits, both to evaluate the effect of exposure and to design and interpret intervention studies.

With respect to the definition of endpoints, further evaluation of the commonly used UESTD physical examination maneuvers is needed to examine their sensitivity, specificity, and reproducibility among examiners. 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 pace (measured as average hourly output) among piece-rate workers.

### Objectives

1. To estimate the 24-month cumulative incidence of upper extremity musculoskeletal disorders among garment workers previously pain-free, as a function of the intensity of occupational exposure to ergonomic stressors.
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. Among those workers previously symptomatic, 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.
4. To estimate the agreement between two-point discrimination testing for median nerve impairment and other symptoms and signs of carpal tunnel syndrome.
5. To estimate the reproducibility between two examiners of UESTD findings obtained by physical examination (including two-point discrimination).
6. To explore whether there is a cross-sectional 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 will now be analyzed. At 24 months from baseline, 198 (90%) 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 will be estimated using both job category and quantitative measures of ergonomic stressors (cycle time and frequency of postures). Among the workers who reported pain, the long-term (24-month) and short-term (6-month) persistence of and recovery from pain will also be estimated both by job category and by exposure level. The probability of remaining employed over 24 months will be calculated, conditional on the presence or absence at baseline of UESTD symptoms or symptoms plus signs, to estimate the magnitude of selection bias resulting from loss to follow-up.

The physical examination findings obtained by the two examiners will be compared, and the agreement between the two-point discrimination test for median nerve impairment and other symptoms and 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 (both regular and overtime), wage basis (25 hourly and 195 piece-rate workers), 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 will be made within piece-rate jobs, using tabulated and logistic regression analysis to compare cases and non-cases on average hourly output.

### **Significant Findings**

The study has just begun. As of September 30, 1989, a statistical applications programmer had been hired and trained. The magnetic data tapes were obtained from storage and mounted; the raw data were read into SAS, and the SAS datasets were cleaned and formatted.

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## Occupational Cancer Surveillance: New Approaches

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Program Area: *Occupational Cancers*  
Grant Number: *7 R01 OH02067-05*  
Start & End Dates: *09/28/84 - 09/29/91*  
Funding Level: *\$154,118 (\$926,545 Cum)*

### Importance to Occupational Safety and Health

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

### Objectives

The long-term goal of this study is to develop and test new hypotheses regarding the occupational etiology of selected forms of cancer. Both cancer incidence data, as the disease outcome measures,

and lifetime work histories will be utilized, complemented by other essential risk factor data associated with the measures of exposure.

The specific aims of this study are:

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

### Methodology

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

### Significant Findings

Preliminary results show excess risk of lung cancer and of cancer of the urinary bladder among specific occupations and industries. These analyses provide risk estimates that are adjusted for cigarette smoking and age at diagnosis. Analysis of usual occupation and industry among lung cancer cases revealed excess risks for farmers, assemblers, production inspectors, mechanics, metal finishers, machine repairers, furnace workers, and enlisted military personnel.

Analysis of risks among black and white men separately revealed that the risk among farmers, assemblers, and production inspectors is concentrated among black males, while the risk among metal finishers, machine repairers, and furnace workers is concentrated among white males.

Additional risk among black males only was observed for painters and dry cleaning workers.

Analysis of occupational risks among bladder cancer cases showed excess risk for all males among electrical workers and farmers, for white males among drivers, and for black males for painters, mechanics, tool and die workers, and production inspectors. Among all women, excess risk of bladder cancer was seen for production inspectors and dry cleaning workers, and among white women for food workers.

A third analysis is underway to investigate the relationship between cigarette smoking (especially age at start and quit smoking, dose and duration of smoking) for four histologic types of lung cancer: squamous cell, adenocarcinoma, large cell, and small cell. These data show a strong relationship between cigarette smoking and each of the four histologic groups, as well as specifying different dose-response curves for each type. It is clear from this analysis that for lung cancer, both occupational and smoking histories must be assessed separately for each of the four cell types to specify different etiologic patterns.

#### Publications

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

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

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## Feasibility Study for an Occupational Cancer Data Base

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Program Area: *Occupational Cancers*  
 Grant Number: *5 R01 OH02284-02*  
 Start & End Dates: *09/28/87 - 09/27/89*  
 Funding Level: *\$5,275 (\$24,815 Cum)*

#### Importance to Occupational Safety and Health

With the constant introduction into the workplace of new processes, substances, and equipment, the monitoring of cancers associated with occupation and industry is an essential part of the effort to prevent occupational cancer. Occupational exposures are estimated to account for approximately 4% of all cancer deaths and probably about 5% of cancer incidence. The collection of complete, accurate, standardized occupation and industry data for cancer patients is difficult and expensive. The results of this project will assist in the development of the most cost-effective method of collecting these data for cancer patients in the California Tumor Registry.

#### Objectives

This was a pilot study to test the effectiveness of a brief questionnaire asking for patients' usual (defined as longest-held) occupation and industry. The reported occupation was compared to the total work history and to any occupation/industry information noted in the patient's medical record.

#### Methodology

Occupation and industry data were gathered on a sample of cancer patients from four test hospitals: a large private hospital, a county hospital, a health maintenance organization (HMO), and a Veterans' Administration hospital. Three different methods of data collection were used.

The primary method of data collection was a brief questionnaire to be completed before or during the patient's admission to a hospital or visit to an outpatient clinic. The questionnaire was designed to be as brief and simple as possible, to be

self-administered, if feasible, or administered by others if the patient was unable to complete it without assistance. In the county hospital and the HMO, patients were given questionnaires by hospital staff at the time of admission or preadmission; in the VA hospital, questionnaires were given to patients on the ward by the ward clerk; in the private hospital, they were given to patients on the ward by study personnel. Since it was not always possible to select cancer patients, questionnaires were also given to some patients whose illnesses were not known.

The second data collection method was a questionnaire to be administered by telephone to the patient at home. The purpose was to obtain a chronological work history which could be compared to the brief occupation and industry statements. This questionnaire was administered to a sample of the cancer patients on whom the brief questionnaire was completed.

The third method was a review of the medical charts of cancer patients, including those for whom both brief questionnaires and chronological work histories were available, to determine how much information was present on occupation and/or industry.

Brief questionnaires were completed for 205 cancer patients. Eighty-five of these patients were subsequently interviewed to obtain a chronological work history. The medical records of 248 cancer patients were reviewed to determine the quantity and quality of any occupation/industry data. All occupation and industry data were coded using the six-digit coding classification of the Bureau of the Census 1980 Census of Population.

### Significant Findings

A brief questionnaire, either self-administered or administered by hospital staff at the time of admission, can be an effective method of obtaining patients' longest-held occupation and industry. After hospitalization for cancer many patients cannot be reached for a telephone interview to obtain a detailed work history.

In this study, 85 cancer patients, who reported their usual occupation and industry on a brief questionnaire at the time of hospitalization for cancer, were interviewed by telephone a few weeks later to obtain their detailed work history. Sixty percent reported job titles that were identical or similar enough to produce exact agreement between the coded classifications of their usual occupation/industry reported on the brief questionnaire and the calculated longest-held job from the job history. Twenty-nine percent of the patients reported job titles which were different

enough to produce different codes for what were actually the same jobs. In two percent, the longest-held job reported in the work history had potentially carcinogenic exposures not associated with the job reported on the brief questionnaire.

Review of the entire work history of each patient showed that 20% had jobs, other than their longest-held job, with potentially carcinogenic exposures. These patients would be misclassified with regard to potentially carcinogenic exposures if only their longest-held jobs were considered.

A total of 248 medical records of cancer patients in the four hospitals were reviewed for mention of occupation and industry. Occupation and industry were noted in 15%, occupation only in 36%, and industry only in 8%, a total of 59% with some type of job information. In the 85 patients for whom a work history had been obtained, comparison of the medical record information with the longest-held job from the work history showed a 46% agreement for occupation and/or industry.

The overall conclusion of this study is that the monitoring of occupation and industry of cancer patients requires that patients' usual occupation and industry be obtained at the time of hospital admission (or at the time of diagnosis for non-hospitalized patients) and that a detailed work history be obtained for a sample of patients as soon as practicable.

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## Relative Health Risks of Diesel Emission Control Systems

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Program Area: *Occupational Cancers*  
Grant Number: *1 R01 OH02611-01*  
Start & End Dates: *01/01/89 - 12/31/91*  
Funding Level: *\$81,993 (\$81,993 Cum)*

### Importance to Occupational Safety and Health

Whole diesel exhaust is regarded as a potential occupational carcinogen by the National Institute for Occupational Safety and Health (NIOSH) but the risk of cancer to exposed workers has not been quantitatively defined. One problem encountered in defining risk is the chemical complexity of diesel exhaust, making it difficult to define exposure. In

this NIOSH-funded study, researchers at Michigan Technological University (MTU) are working with researchers at the Bureau of Mines (BOM) to define aspects of the chemical nature and biological activity of diesel particulate matter (DPM) collected in underground mines. Data for both DPM and semi-volatile organics will be collected from diesel engines operated with and without DPM emission control devices under laboratory and in-mine conditions. Together, these data will be utilized to more effectively evaluate potential health impacts of diesel exhaust and the effects potential emission controls will have on contaminants in the underground mine atmosphere.

### Objectives

The overall objectives of this project are (1) to obtain estimates of diesel pollutant levels in underground 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, both in laboratory tests and in mines. To date, the project focus has been on the study of underground coal mines.

### Methodology

In-mine samples are being collected using Hi-volume samplers equipped with inertial impactors to collect size-differentiated particulate samples. The particles present on the back-up, 203 x 254-mm filters are  $\leq 1 \mu\text{m}$  in size and are considered to be primarily of diesel origin. Samplers are placed at two locations in each of the dieselized mines: the section intake and the haulageway. The soluble organic fraction (SOF) is removed from the particulate on the filters by Soxhlet extraction with dichloromethane. The daily extracts from all filters at each sampling location in a mine are pooled to reflect average levels over each day's entire sampling period.

Laboratory samples are being collected at the BOM Twin Cities Research Center diesel engine test facility. Diluted DPM exhaust samples are collected on 508 x 508-mm filters followed by semi-volatile organics samples collected on XAD-2 resin (XOC) for transient engine operation. Only filter samples are collected during steady-state operation. As with the in-mine samples, the organic material associated with both types of media is removed by Soxhlet extraction with dichloromethane.

All SOF and XOC are handled for PAH quantitation and biological activity assessment using the same procedures. PAH and nitro-PAH

fractions of the SOF and XOC are obtained from a two-column (Florisil and  $\text{C}_{18}$ ) clean-up procedure and analyzed by HPLC with fluorescence detection. The PAH and nitro-PAH chosen for quantitation due to their known or suspected health effects include fluoranthene, chrysene, benz[a]anthracene, benzo[a]pyrene, 1-nitropyrene, 2-nitrofluorene, 3-nitrofluoranthene, and 4-nitrobiphenyl. Sulfate levels are determined by ion chromatography of aqueous extracts from the filters following their Soxhlet extraction for SOF removal. Unfractionated extracts plus some fractions are tested for biological activity using the microsuspension version of the Ames assay. Coal samples from each mine are extracted and assayed for PAH levels and activity. Data associated with the laboratory generated samples can then be converted to estimated in-mine concentrations in order to better evaluate potential impacts of certain engine operating conditions and emission control systems.

### Significant Findings

To date, approximately 80 filter samples have been collected from four underground dieselized coal mines in the eastern and western United States as well as approximately 50 filter samples and 30 XAD-2 resin samples from the BOM laboratory test facility. Emphasis during this first project year was placed on the determination of DPM, SOF, and sulfate levels associated with the filters and the levels of semi-volatile organics collected on the XAD-2 resin.

Analyses of SOF-associated mutagenicity from one of the coal mines where samples were collected over four working days have been completed. Analyses of PAH from the same samples are in progress. To our knowledge, these are the first such data available for levels over a work-week and from more than one in-mine location. The detected SOF mutagenicity is direct-acting in nature which is typical of DPM-associated organics. In contrast, the coal extracts displayed no activity. There is little difference in SOF mutagenicity (revertants/ $\mu\text{g}$ ) between the intake and haulageway samples. However, the haulageway revertant/ $\text{m}^3$  values are nearly ten times those at the intake due to higher %SOF and DPM levels ( $\text{mg}/\text{m}^3$ ). The intake area usually has lower DPM levels ( $\text{mg}/\text{m}^3$ ) and wider fluctuations in both DPM and revertant/ $\text{m}^3$  levels. Some mining practices on these sampling days have been tentatively correlated with the specific changes in these levels.

The BOM laboratory test facility samples were collected during transient and steady-state operation with and without a catalyzed diesel particulate filter using a low sulfur (0.03 wt.%) diesel fuel.

Extraction of the samples into the various components indicates that this catalyzed filter reduces the DPM, SOF, and XOC levels during transient operation 91%, 99%, and 82%, respectively. The sulfate concentrations increased nearly 400% but were still below 0.80 mg/m<sup>3</sup>. These samples will be further fractionated and analyzed for biological activity and chemical characterization.

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## Biologic Monitoring/Risk Assessment in an Exposed Cohort

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Program Area: *Occupational Cancers*  
Grant Number: *1 R01 OH02647-01*  
Start & End Dates: *09/30/89 - 5/30/90*  
Funding Level: *\$30,415 (\$30,415 Cum)*

### Importance to Occupational Safety and Health

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

Results of this pilot study and the proposed 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 current pilot study was undertaken to demonstrate, by evaluating a small number of subjects in a Chinese occupational cohort at high-risk for bladder cancer, the feasibility of conducting a larger study we proposed in the same cohort. The objectives of the larger study are: (1) to identify and measure the various endogenous and exogenous risk factors and biological markers in order to differentiate individuals and subgroups according to their risk for bladder cancer; and (2) to evaluate the usefulness of various biological markers as discriminators of risk and as intermediate endpoint markers. We recognize that the small sample size will limit the statistical significance of the results of the pilot study, but the overriding objectives are to demonstrate our ability to conduct the screening program in China and to confirm the logistics of the handling and shipment of samples for laboratory studies in the U.S.

### Methodology

In the pilot study, thirty members of a previously identified cohort of workers (N = 2,005) exposed to benzidine will be screened. An equal number of unexposed controls will be screened identically. The study is limited to those from only one (the Tianjing province in China) of the five localities to be included in the later study in order to expedite completion of the pilot study in a relatively short frame and to involve a smaller number of field personnel.

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 (100 cc) and blood (2 @ 10 ml each) samples. Diagnostic followup (as described in the protocol) will be included for subjects whose initial screening results meet certain criteria.

As described in the original protocol, quality control, personnel training and standardization of study methods, recordkeeping, and data management are important considerations in both the 8-month pilot study and the later multicenter human population study.

#### Significant Findings

Since the grant was not funded until September 30, 1989, there are no significant findings to report during FY89.

### New Method for Occupational Cancer Surveillance

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Program Area: *Occupational Cancers*  
Grant Number: *1 K01 OH00076-01*  
Start & End Dates: *07/15/89 - 07/14/92*  
Funding Level: *\$32,314 (\$32,314 Cum)*

#### Importance to Occupational Safety and Health

An important goal of occupational health is the prevention of occupational cancers. A critical step toward that goal is the development of biomarkers of exposure and response to workplace carcinogens. Such biomarkers should allow identification of those individuals who are at an early stage of developing

neoplastic disease so that the disease process can be aborted. This research proposes to demonstrate the utility of a newly developed biomarker, based on the detection of oncogene-encoded proteins in serum, in contributing to the early detection of biological response to workplace carcinogen exposure.

#### Objectives

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

#### Methodology

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

#### Significant Findings

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

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Brandt-Rauf PW, Smith S, Perera FP, Niman HL, Yohannan W, Hemminki K, Santella RM: Serum Oncogene Proteins in Hazardous Workers. Journal of the Society of Occupational Medicine, in press, 1989

Brandt-Rauf PW, Smith S, Perera FP: Molecular Epidemiology and Environmental Carcinogenesis of the Lung. Problems in Respiratory Care, in press, 1989

Brandt-Rauf PW: Serum Screening for Oncogene Proteins in Occupationally Exposed Workers. Journal of Cancer Research and Clinical Oncology, in press, 1989 (Abstract)

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## Role of Oxidants in Hematopoietic Toxicity

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

### Importance to Occupational Safety and Health

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

### Objectives

The hypothesis being tested is that oxidants generated by phagocytes in the bone marrow play a prominent role in some mechanisms of chemically-induced hematopoietic toxicity. It is the overall aim of this project to investigate the role of oxidants in hematopoietic toxicity by using benzo[a]pyrene-7,8-dihydrodiol (BP-diol) and hydroquinone (HQ), metabolites of BP and benzene, respectively, as model chemicals to study the metabolism of xenobiotics by mammalian bone marrow derived from strains of mice with known

susceptibility (DBA/2) and resistance (C57B1/6) to orally administered BP.

### Methodology

1. Chemiluminescent probing, superoxide anion production and myeloperoxidase activity will be used to compare oxidant generation between DBA/2- and C57B1/6-derived bone marrow phagocytes.
2. Activation of BP-diol to a chemiluminescent species and an intermediate(s) which covalently binds to endogenous DNA will be characterized and compared between the two strains of mice.
3. Target cell population(s) within the bone marrow will be identified using *in vitro* cell survival and colony forming unit (CFU) techniques.
4. Primary *in vitro* cultures of various bone marrow derived cells will be used to biochemically characterize putative protective enzymes in various cell populations of the bone marrow.

### Significant Findings

DBA/2 mice, a strain with non-inducible P-450 systems, has been shown to be more susceptible than C57B1/6 mice to the bone marrow toxic effects of both BP and benzene. We have compared the oxidant generation of neutrophilic cells isolated from femurs of male DBA/2 and C57B1/6 mice. Oxidant generation of 12-*o*-tetradecanoylphorbol-13-acetate (TPA)-stimulated neutrophilic preparations was assessed by superoxide generation and oxidant-dependent chemiluminescence (CL) from luminol (myeloperoxidase-dependent) or lucigenin (superoxide-dependent). Cells from DBA/2 mice demonstrated increased oxidant generation as compared to those from C57B1/6. Similarly, a twofold enhancement of oxidant-dependent CL from BP-diol was observed with TPA-stimulated neutrophilic cells from DBA/2 mice as compared with cells from C57B1/6 mice. This BP-diol-dependent CL was inhibited by the addition of azide or superoxide dismutase. Additionally, 25% greater covalent binding of BP-diol, the proximate carcinogenic metabolite of BP, to DNA was observed in the presence of TPA-stimulated neutrophils from DBA/2 mice (6.2 pmol/mg DNA) compared with cells from C57B1/6 mice (4.7 pmol/mg DNA). These results suggest that the increased risk of DBA/2 mice for BP-induced leukemia may be related to their greater ability to generate oxidants which could participate in the

activation of carcinogens as well as promote the development of bone marrow neoplasms.

Another area under investigation with respect to mechanisms of chemically-induced bone marrow toxicity is the role of protective enzymes within the target organ, bone marrow. Quinone metabolites are common to both BP and benzene, and quinone reductase (QR) is an important enzyme in protecting cells against the toxic effects of quinones. Thus, whole bone marrow preparations from C57B1/6 and DBA/2 mice were examined for their QR activity and a significant difference in QR activity was observed between these two strains of mice. Cells from C57B1/6 mice had approximately 1.5-fold more QR activity than those from DBA/2 mice. This difference in basal QR activity was also found in bone marrow primary stromal cells, cells which have been shown to be an important target of hydroquinone toxicity within the bone marrow. C57B1/6-derived stroma had approximately twice the basal QR activity of DBA/2-derived stromal cells. This difference in basal QR activity between cells from C57B1/6 and DBA/2 mice was reflected in their relative susceptibilities to cellular toxicity induced by two quinone-generating compounds, tert-butylhydroquinone (tBHQ) and hydroquinone (HQ); DBA-derived cells, having lower QR activity, were more sensitive to both tBHQ- and HQ-induced toxicity. Recent studies have shown that the *in vitro* induction of QR can protect hepatoma cells against the toxicity of a number of quinone xenobiotics. We have extended these observations and have demonstrated in this study that prior induction of QR by 1,2-dithiole-3-thione (DTT) also protects bone marrow stromal cells from both C57B1/6 and DBA/2 mice against HQ-induced toxicity. Studies to assess *in vivo* DTT induction of QR within the bone marrow compartment are in progress.

We next examined if peroxidases could potentiate toxicity to stromal cells since HQ had been shown to be metabolically activated to an electrophile by both horseradish peroxidase (HRP) and myeloperoxidase (MPO), the peroxidase of myeloid cells. The toxicity of HQ to stromal cells was potentiated in the presence of H<sub>2</sub>O<sub>2</sub> and either HRP or human MPO, such that nontoxic  $\mu$ M concentrations of HQ became toxic. We are presently investigating if bone marrow-derived neutrophils, which contain the majority of MPO in bone marrow, can also potentiate HQ toxicity to bone marrow stromal cells.

### Publications

Twerdok LE, Rembish SJ, Trush MA: Studies with 1,2-dithiole-3-thione as a Chemoprotector in Mouse

Bone Marrow Stromal Cells. *The Toxicologist*, in press, 1990

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

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

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## Activation of H-Ras Oncogene by N-Heterocyclic Aromatics

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Program Area: *Occupational Cancers*  
Grant Number: *1 R03 OH02657-01*  
Start & End Dates: *08/01/89 - 07/31/91*  
Funding Level: *\$16,000 (\$16,000 Cum)*

### Importance to Occupational Safety and Health

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

### Objectives

The objective of this study is to determine whether mouse skin tumors initiated with DBA or DBC contain an activated H-ras oncogene. Mouse skin tumors initiated with the polycyclic aromatic

compound 7,12-dimethylbenz(a)anthracene (DMBA) will be used as a positive control as many different investigators have consistently shown this compound to activate the H-ras gene. The nature of the activating mutations will also be determined; in specific, the exact points of mutations and the location in the H-ras gene will be determined.

### Methodology

Initially, DNA is obtained from mouse skin tumors by pulverization of the tissue in liquid nitrogen, digestion, and extraction with phenol/chloroform. Purification of the DNA is achieved by centrifugation through a CsCl gradient.

The tumor DNA is then screened for the presence of an activated H-ras gene by the NIH3T3 transfection assay. This involves introducing the tumor DNA into NIH3T3 cells by the calcium phosphate co-precipitation method. The assay is considered to be positive if transformed foci result, indicating that oncogenic sequences of DNA were taken up by the NIH3T3 cells. The DNA is then further analyzed to determine the nature of the H-ras mutations.

It was initially proposed that the H-ras protein, p21, would be analyzed for changes in its electrophoretic mobility, as these have been shown to correlate specifically with mutations in the two "hot spots" of the H-ras gene, codons 12 and 61. This technique involves isolating proteins from the tumor tissue, separating them by SDS-polyacrylamide gel electrophoresis, transferring them to nitrocellulose, and probing them with an antibody to p21. Detection of the antibody-p21 complexes is accomplished by an enzymatic reaction. However, this approach has proven difficult and may not be followed. Recent reports in the literature have revealed significant differences in the success of this assay depending on the anti-p21 antibody which is employed. Therefore, this technique will be tried again using a different antibody.

The DNA from NIH3T3-transfection positive samples may be analyzed by a variety of techniques, including analysis of restriction fragment length polymorphisms, polymerase chain reaction and subsequent synthetic oligonucleotide hybridization, or direct sequencing of the "hot spots" of the H-ras gene.

### Significant Findings

Initial work focused on the NIH3T3 transfection assay. DNA has been successfully isolated from tumor tissue and transfected into NIH3T3 cells, resulting in transformation. The plasmid pSV2neo

(which confers resistance to the neomycin analogue G418) was co-transfected with the tumor DNA to ensure a successful transfection. Statistical analysis is in progress.

Studies were also performed to assess changes in p21. Proteins isolated from mouse skin tumors were subjected to Western blotting as described above. Preliminary experiments have suggested that a sample from a DBA-induced tumor contains a mutant form of p21 which migrates faster than normal p21, suggesting that a mutation in codon 61 exists.

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## Explosion Hazards Related to Combustible Dusts

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Program Area: *Traumatic Injuries*  
Grant Number: *2 R01 OH01122-07A1*  
Start & End Dates: *01/01/81 - 03/29/92*  
Funding Level: *\$204,109 (\$784,178 Cum)*

### Importance to Occupational Safety and Health

It is well known that finely divided combustible material, whether suspended in air or layered on surfaces, is capable of supporting a rapidly occurring combustion process which is commonly referred to as an explosion. The severity of such explosions compare favorably with those resulting from the combustion with air of usually recognized flammable gases such as methane and propane. 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 alone in 1988, there were 11 dust explosions resulting in 11 injuries and 8 deaths, while for fiscal 1989 the statistics are 10 explosions, 5 injuries, and 2 deaths. Through the first quarter of fiscal 1990, there have been 4 explosions resulting in 2 injuries and 0 deaths. This situation is much improved from the late 1970's and early 1980's. 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 their subsequent litigation. This research effort is the point of contact within the United States for cooperative dust explosions research which is being funded by the U.S. Department of Agriculture in Poland and which will be funded in the Soviet Union, which effectively makes available additional results actually obtained from industrial scale facilities.

### Objectives

The purpose of this research project is to quantitatively characterize the explosion hazard

represented by suspended and layered combustible dust. While much testing concerning the explosive behavior of combustible dusts has been done for many years, these results are apparatus-dependent and provide no data for deflagrations which can be used in the computer modelling of scenarios applicable to large scale dust explosions. These results fail to characterize a fundamental physical quantity, the burning velocity, and none of them pertain to the secondary explosions which result from layered dust accumulations. None of the testing procedures determine if the dust can sustain a detonation and subsequently determine the parameters associated with such. Using specially developed facilities, measurements are made which describe the fundamental aspects of dust combustion (laminar and turbulent burning velocities, denotation, velocity, reaction zone thickness, etc.) as a function of the parameters describing the initial conditions for the dust (chemical composition, size, shape, concentration, moisture content, premixedness, turbulence parameters including intensity and scale, etc.) Analytical efforts directed at the development of models which explain the observed phenomena are continuing.

### Methodology

Two unique pieces of experimental equipment were developed to measure the fundamental data required and to avoid the criticisms associated with previously acquired dust explosion test data which were obtained using a standard test apparatus. 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 recently extended Flame Acceleration Tube (FAT) which consists of seven continuous segments of 3000 psi working pressure steel tubing with a total length of 231 ft. and an inside diameter of one foot. It is closed at one end and open at the other. A controlled thickness and width dust layer is placed along the bottom of the tube, and it is then ignited by the combustion of a presuspended dust cloud (primary explosion) in the first twelve feet of the closed end. The history of the resulting combustion process as it accelerates toward the open end is monitored using regularly spaced appropriate instrumentation. In both of these facilities, the burning velocity and the post-combustion conditions

are measured as a function of parameters characterizing the dust and pre-combustion thermodynamic conditions. Additionally, a horizontal and a vertical detonation tube have been reactivated. 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 has been constructed which allows the suspension of a dust particle in a controlled environment where it may be ignited and its subsequent combustion observed.

#### Significant Findings

For the facilities that are used to observe the turbulent combustion of suspended dust/air mixtures, more results have been obtained concerning the intensity and scale of the turbulence which has such a great effect on the combustion process. The scale and intensity achievable may not be adequate to duplicate actual industrial accident conditions. The burning velocity obtained from these facilities for methane, cornstarch, and aluminum shows the strong effect of the turbulence, particle size, and equivalence ratio. For the layered dust combustion, as a result of the much larger length to diameter ratio now available with the facility, 240, much more extreme post-combustion conditions are achieved—bordering on detonation. The furnace facility constructed to investigate the burning rate of individual dust particles has produced data showing that the burning time is related to particle area, and that for small enough particles, there is no gas phase diffusion flame. The analytical model describing layered dust flame propagation is able to reasonably reproduce the time and distance dependence of measured quantities such as gas pressure, velocity, and temperature.

#### Publications

Sichel M: Numerical Modelling of Heterogenous Detonations. In Numerical Approaches to Combustion Modelling, (eds. ES Oran, J Boris),

American Institute of Aeronautics and Astronautics, in press, 1989

Leisch SO, Kauffman CW, Sichel M: The Smoldering Combustion of Cellulosic and Starch Dusts. Proc of the Int Conf on the Physical and Chemical Processes Occurring in a Burning Cigarette, R.J. Reynolds Tobacco Co., Wisconsin Salem, NC, 1987

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

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### An Epidemiologic Study of Injuries in Firefighters

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

#### Importance to Occupational Safety and Health

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

#### Objectives

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

### Methodology

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

### Significant Findings

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

### Publications

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

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## Reduction of Occupational Injury Deaths in Rural Colorado

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Program Area: *Traumatic Injuries*  
Grant Number: *5 R01 OH02601-02*  
Start & End Dates: *09/30/88 - 09/29/91*  
Funding Level: *\$158,023 (\$296,518 Cum)*

### Importance to Occupational Safety and Health

Fully half of the occupational injuries in Colorado that result in death occur in rural areas where only 20% of the workforce resides. Thus,

rural occupational injury deaths constitute a major public health problem in Colorado, and if this pattern holds in other states with rural areas, it represents a public health problem nationally.

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

### Objectives

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

### Methodology

Occupational injury deaths are ascertained primarily by linkage of workers' compensation claims (WC), OSHA case reports, and death certificates (DC). Additionally, motor vehicle traffic accident reports are linked for occupational traffic deaths. Injury rates by industry and region are calculated based on workforce estimates from the Bureau of Economic Analysis' (BEA) Regional Economic Information System.

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

Injury severity is determined by assigning Injury Severity Scores (ISS) using all available information on deaths (coroner's reports, autopsy reports, emergency room records, and hospital records) and on seriously injured survivors (hospital summaries and discharge diagnoses). Occupational injury hospitalizations will be identified from method of payment (workers' compensation) on the statewide uniform hospital discharge data set from the

Colorado Hospital Association. The serious, nonfatal, hospitalized injuries will be initially identified by computing ISS scores from discharge diagnoses via software developed at the Johns Hopkins University. Analysis will include calculation of preventable death rates by region and, by incorporating survivors with high ISS scores, calculation of trauma care effectiveness.

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

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

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

### Significant Findings

Firm size is an independent risk factor for occupational injury fatality. In Colorado, preliminary estimates show that employees of small firms (<20 employees) have six times the risk of employees of firms size 500+.

Injury Severity Scores (ISS) could be assigned to 79% of occupational injury deaths in Colorado for 1986 and 1987. Among those deaths without ISS, 57% were because of the nature of the injury, and only 43% because of insufficient information, the latter accounting for only 9% of total deaths.

Underestimate of injury severity is introduced if deaths without either autopsy or health facility reports are excluded, since ISS could be assigned to the great majority of these deaths (69%) and in 81% of those with ISS the score was 75.

Significantly higher injury severity occurred with rural region deaths compared to Denver metro. For example, 69% of rural deaths had ISS of 75 compared to 35% of Denver metro deaths ( $p < .01$ ). Preliminary interpretation is that this difference is attributable primarily to the greater severity of occupational injuries in rural Colorado, suggesting that the greatest emphasis should be on pre-event and event factors in directing prevention efforts.

A most encouraging temporal trend in work-related MVA fatalities has been observed as the proportion of alcohol-associated fatalities has decreased from 27% in 1982-84 to 11.5% in 1985-87. This has been accompanied by a 29% reduction in number of fatalities while non-MVA fatalities have decreased only 5%.

An agreement was reached between the Colorado Department of Health and Colorado OSHA to conduct joint case investigations. This is apparently the first time such a cooperative arrangement has been made, and the experience may contribute to changes in policy at the national level. Since April 1989 our industrial hygienist/safety staff person has conducted over 20 investigations. These included 12 joint investigations with OSHA personnel. No difficulties have been encountered in augmenting the OSHA procedures with those of the FACE protocol.

Emerging strategies to reduce rural occupational injury deaths are that (1) large employers should consider development of a technical assistance program in workplace training and safety for small employers in the same industry, especially in rural areas; (2) major emphasis should be directed at primary and secondary prevention efforts; (3) the success of reducing the proportion of alcohol-associated, work-related MVA fatalities in 1985-87 compared to 1982-84 should be communicated to industry; and (4) augmented resources are needed for the OSHA voluntary and technical assistance program to enable safety training of high risk industry groups in rural areas.

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### Evaluation of a Database for Injury Surveillance

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Program Area: *Traumatic Injuries*  
Grant Number: *5 R03 OH02579-02*  
Start & End Dates: *09/15/88 - 09/14/90*  
Funding Level: *\$19,225 (\$37,236 Cum)*

### Importance to Occupational Safety and Health

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

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

### Objectives

The objectives of this study are to:

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

### Methodology

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

### Significant Findings

A total of 1,601 injury records were on the hospital discharge database for 1985 and 1986. Eighty-two percent (1,305) of these records were returned by New Jersey hospitals with patient name and address. A 25% random sample of the 980 finger amputation records was chosen to approximate the numbers of other frequent injuries. The total numbers and percentages of 586 selected, unique cases with identifying information by injury type are: finger amputation (207, 35.3%); thumb amputation (160, 27.3%); crush injury of the lower limb (143, 24.4%); toxic effects of metals (45, 7.7%); and eyeburns (31, 5.3%).

Sixty-six records returned by hospitals were chosen at random to conduct a pilot study of the telephone interview. Twenty-one of 66 (32%) persons were located and consented to be interviewed. Twelve of 21 persons (57%) interviewed reported a work-related injury.

The pilot study data from 21 completed interviews were examined for the amount of agreement between work-relatedness of injury by self-report, and the presence of workers' compensation in the primary payor code on the UB-82 database. The percent agreement was 91% and the agreement beyond chance (Kappa) was 0.82, which is interpreted as excellent agreement.

Based on our pilot study results, we expect to locate and interview 32% of 586 potential subjects, amounting to 187 completed interviews by the end of the project study period.

## The Effect of Localized Fatigue on Postural Stability

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Program Area: *Traumatic Injuries*  
Grant Number: *1 R03 OH02653-01*  
Start & End Dates: *04/01/89 - 03/31/91*  
Funding Level: *\$20,675 (\$20,675 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.

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### Incidence of Work-Related Injury

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Program Area: *Traumatic Injuries*  
Grant Number: *1 R03 OH02659-01*  
Start & End Dates: *06/01/89 - 05/31/91*  
Funding Level: *\$21,391 (\$21,391 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 1982-1986.

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

Work-related ER visits at the study hospital included in NEISS average over 600 per year, while Workers' Compensation lost-time claims average a little over 300 per year. At most, 100 of these records refer to the same people, so the unduplicated total is no more than 800 injuries per year. An estimated 250 visits per year at the second hospital (based on a 1/6 sample) lead to an estimate of about 1,050 injury visits per year. Preliminary results of the record abstracting at the principal hospital indicate that NEISS misses about 25% of work-related injuries treated at the principal hospital, so that the estimated total of ER visits is closer to 800 per year, and the total of ER visits plus workers' compensation claims is about 1,250 per year. BLS rates applied to the employed

population of Athens County lead to an estimate of about 850 medically treated injuries per year.

Current work involves matching the samples of ER records at the two hospitals to Workers' Compensation records and refining the matching criteria for the two sets of data. Also, the definition of the employed population is being refined further through field work and cooperative efforts with the Ohio Industrial Commission.

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## Stress Effects of Human-Computer Interactions

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Program Area: *Cardiovascular Diseases*

Grant Number: *1 R01 OH02614-01A1*

Start & End Dates: *09/01/89 - 8/31/90*

Funding Level: *\$26,630 (\$26,630 Cum)*

### Importance to Occupational Safety and Health

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

### Objectives

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

### Methodology

A "treatments by levels" experimental design will be used. Subjects will be typed by the Structured Interview. Thirty Type A subjects will be assigned to either a constant or variable throughput condition, as will 30 Type B subjects. Subjects will operate a synthetic data retrieval task while blood pressure, heart rate, masseter, and corrugator supercillii responses are assessed. In addition to a 30-min resting baseline session not including task performance, a performance session will consist of 10 min of resting baseline, 30 min of task performance, and 10 min of resting baseline. Initial baseline means will be used as covariates for ANCOVAs with means for all baseline and task components of the performance session.

### Significant Findings

Since the research grant commenced in September, 1989, efforts have necessarily been directed toward preparing the research facility. No data have yet been collected.

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## Occupational Risks of Pesticide Exposure for Females

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Program Area: *Disorders of Reproduction*  
Grant Number: *5 R01 OH00835-11*  
Start & End Dates: *09/01/88 - 08/31/91*  
Funding Level: *\$47,743 (\$473,888 Cum)*

### Importance to Occupational Safety and Health

The significance of reproductive hazards in the workplace has been underscored by the fact that the National Institute for Occupational Safety and Health (NIOSH) ranks it as a leading work-related hazard. The manufacture of pesticides is a major industry in this country. Exposure to pesticides is a fact of life for many workers both skilled and unskilled. Most employees and employers are acutely aware of the potential hazards of exposing a pregnant woman to a toxic substance. However, minimal attention has been directed toward the potential hazardous effects that exposure of a non-pregnant female might have on the future fertility of this individual. This investigation examines pesticide exposure of both the pregnant and non-pregnant female. These systems need to be evaluated so that appropriate safeguards can be implemented to protect not only the pregnant female but also the non-pregnant female who will one day desire to become pregnant.

### Objectives

Estrogen is a major steroid secreted by the ovary, and it is intimately involved in the normal progression of sex cell differentiation, growth, and ovulation. Any disturbance in the synthesis, secretion, or target tissue response to this hormone can result in severe impairment of normal physiological activities of the ovary with potentially devastating effects on present and future fertility. Pesticides such as DDT, chlordecone (Kepone), and methoxychlor are pesticides that have been shown to possess estrogenic activity. The present project is designed to characterize some of the reproductive hazards that confront both non-pregnant and pregnant females engaged in occupations which

subject them to potential exposure to estrogenic pesticides.

### 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 dosages of chlordecone, methoxychlor, estradiol-17 $\beta$ , or sesame oil. After four weeks of exposure, the ovaries were removed and prepared for histological evaluation and tabulation of the follicle populations. In the experimental procedures involving exposure of pregnant females, mice were exposed daily to the pesticide from Day 6 - Day 15 of gestation. Offspring were evaluated at parturition as to their number, sex, weight, and any visible external malformations. Female offspring 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 was similarly evaluated to detect any residual effects remaining following the initial exposure.

### Significant Findings

Histological examination of ovaries of females exposed to 0.25 mg chlordecone for four weeks revealed that there was a reduced number of healthy large and medium-sized follicles and a large number of atretic preovulatory follicles. This is the immediate pool of follicles to be selected for ovulation. In fact, when these animals were induced to ovulate by exposure to exogenous gonadotropins, they ovulated a significantly reduced number of ova, if at all. This fact, plus the already observed decrease in the pool of eggs ready for ovulation, certainly reveals that such a toxicant can affect the fertility of an exposed female.

Exposure of pregnant mice to chlordecone did not elicit any visible morphological aberrations; however, those females' offspring who were exposed prenatally demonstrated an advanced time for vaginal opening. Cross-fostering studies revealed that the early onset of vaginal opening was entirely dependent on prenatal exposure to chlordecone and not to postnatal exposure via lactation alone or in combination with prenatal exposure.

Data obtained from methoxychlor (MXC)-exposed non-pregnant females revealed that the ovaries of exposed mice weighed significantly less than controls and there was increased atresia of large preovulatory follicles. Ultrastructural observations revealed increases in lipid accumulation in ovarian interstitial cells and theca

cells of mice exposed to 5.0 mg MXC and in those treated with estradiol. This would suggest that these cells have the inability to synthesize and secrete steroids. Thus, both chlordecone and MXC appear to exhibit effects closely resembling those of estrogen.

#### Publications

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

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

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

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

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## Effects of 27 MHz Radiation on Somatic and Germ Cells

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Program Area: *Disorders of Reproduction*  
Grant Number: *5 R01 OH02148-05*  
Start & End Dates: *09/30/88 - 09/29/90*  
Funding Level: *\$135,956 (\$622,836 Cum)*

### Importance to Occupational Safety and Health

Characterization of the effects of 27-MHz RF radiation on mammalian somatic and germ cells is essential in defining basic aspects of potential health effects of this most prominent source of occupational RF exposure. Thresholds and dose responses may be applied to an assessment of the adequacy of present RF occupational protection procedures and serve as a basis for the design of future experimental studies.

Findings to date provide firm evidence that RF radiation directly interacts with living systems resulting in functional alterations that are not indirect effects of heating. These findings are significant since occupational RF exposure standards are based upon the premise that RF bioeffects are due to tissue heating. Thus, concepts such as limitations of exposure based on time-averaged RF intensity must be re-examined. RF effects on human lymphocytes and glioma cells (viz altered mitotic effects 3- to 5d postexposure) are of significance since they suggest the possibility of cumulation of RF-induced cellular alterations. Biphasic dose-responses provide a possible explanation for the apparently contradictory results of previously reported RF bioeffects studies. Dose-response data should also prove of value in determining interaction mechanisms.

### Objectives

The principal objective is to determine cellular effects dose thresholds and dose-response relations for continuous wave (CW) and pulse-modulated (PM) 27-MHz RF radiation exposures at intensities encountered in the workplace. By comparing effects 27-MHz RF with effects of exposure to 2450 MHz,

the role of frequency will be determined. Precise control of exposure conditions, such as temperature, will permit testing hypotheses regarding the mechanisms of RF-induced alteration of mammalian somatic and germ cells.

### Methodology

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

### Significant Findings

A single 2h isothermal ( $37 \pm 0.2^\circ\text{C}$ ) exposure to either 27- or 2450-MHz RF radiation induces biphasic dose-dependent alterations in human lymphocyte mitogenesis 3d after exposure, or in DNA and RNA synthesis in glioma (LN71) cells 1, 3, or 5d after exposure. The threshold specific absorption rate (SAR) for RF effects on lymphocytes is approximately 5W/kg. The threshold for glioma alterations is less than 5W/kg. Exposure of either cell type to SARs of <50W/kg stimulated biosynthetic processes, whereas exposure at >50W/kg suppressed cellular activity. 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 occur during G<sub>0</sub>/G<sub>1</sub> phase. A highly statistically significant reduction in the ability of mouse spermatozoa to fertilize mouse ova occurred following a 1 h exposure of sperm at  $37 \pm 0.2^\circ\text{C}$ . RF exposure at SARs in the range of 5- to 200W/kg had no detectable effect on cell viability or morphology.

### Publications

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Cleary SF, Liu LM, Merchant RE: Glioma Proliferation Modulated *In Vitro* by Isothermal Radiofrequency Radiation Exposure. *Radiation Research*, in press, 1990

Cleary SF: Biological Effects of Radiofrequency Electromagnetic Radiation. Chapter 10, *Biological Effects and Medical Applications of Electromagnetic Fields*, (ed. O Gandhi), Prentice Hall, Englewood Cliffs, New Jersey, in press, 1990

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Liu LM, Cleary SF: Effects of 2.45 GHz Microwave and 100 MHz Radiofrequency Radiation on Liposome Permeability at the Phase Transition Temperature. *Bioelectromagnetics* 9:249-257, 1988

Cleary SF: Biological Effects of Non-ionizing Electromagnetic Radiation. In: *Encyclopedia of Medical Devices and Instrumentation*, (ed. JG Webster), J Wiley & Sons, New York, pp. 274-303, 1988

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## Adverse Reproductive Events and Electromagnetic Radiation

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Program Area: *Disorders of Reproduction*  
Grant Number: *1 R01 OH02373-01A1*  
Start & End Dates: *09/30/88 - 09/29/89*  
Funding Level: *\$169,560 (\$169,560 Cum)*

### Importance to Occupational Safety and Health

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

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

### Objectives

To determine the risk of reproductive loss and major/minor anomalies among PTs and their offspring, female PTs are being surveyed by mail. The reproductive experience of women and EMR exposure 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 1500 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 by another questionnaire for the third mailing. From our experience during the pilot study, doing this increases the completion rate for the questionnaire and also reduces the number of individuals with whom we have no knowledge of having made contact. A seven percent recent sample of nonresponders will be contacted by telephone and will be queried on their reasons for nonresponse. The characteristics of nonresponders will be compared to those among respondents in order to assess any differences in the two populations. Reproductive events among PTs ever exposed to EMR or exposed during their pregnancies will be compared to those without EMR exposure. The reproductive events to be considered include fertility, fetal loss, and major/minor anomalies among the offspring. Should a problem be identified among PTs exposed to EMR, more detailed studies will be planned.

### Significant Findings

The data for the study are still being collected. As of November 6, 1989, a total of 42,326 PTs have been contacted by mail. Of these 11,408 women reported having had children or having tried to become pregnant; 7,270 reported never having tried; and 1,529 refused to complete the questionnaire. Sixty-two individuals have died or moved to another country. An additional 4,215 individuals had nonusable addresses. To date 3,695 individuals have outstanding address corrections for whom we have not received a response and may not make contact.

## Prenatal Lead Exposure and Skeletal Growth

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Program Area: *Disorders of Reproduction*

Grant Number: *5 R03 OH02376-02*

Start & End Dates: *05/01/87 - 04/30/90*

Funding Level: *\$21,003 (\$43,653 Cum)*

### Importance to Occupational Safety and Health

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

### Objectives

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

### Methodology

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

### Significant Findings

The significant findings were (1) reduced food intake, not lead exposure, during the first week of lead exposure was the primary determinant of reduced body and skeletal growth (body weight and tail length) in lead-exposed weanling rats (2) persistence of reduced growth in the same lead-exposed rats was not due to a continuous adverse lead effect on body weight, but through a persistent high correlation between regular growth measurements taken over time, (3) maternal lead

exposure had a subtle negative effect on fetal body weight when intrauterine position and sex variables were used along with litter size in the analysis, (4) a greater degree of lead-related growth retardation was found when maternal lead exposure was continued during lactation than when maternal lead exposure was terminated at parturition, (5) continuous maternal lead exposure (prior to mating, during gestation and lactation) caused the greatest degree of weanling offspring growth retardation relative to growth retardation in prenatal-only or lactation-only lead-exposed weanlings, (6) lead altered endochondral bone growth in the epiphyseal growth plate of the proximal tibias in pre- and postnatally lead-exposed weanlings, and (7) whereas the observed lead-related alterations in endochondral osteogenesis appeared to be based on the co-mineralization of lead with calcium, lead-related alterations in endochondral chondrogenesis appeared to be mediated through a lead-related effect on growth plate cartilage matrix maturation. The findings obtained with an ectopic endochondral bone matrix induction system showed that lead applied locally altered normal endochondral mineralization by co-mineralizing with calcium, independently of ectopic bone cellular activity. The same system demonstrated that lead caused a reduction in growth plate cartilage matrix proteoglycans and glycosaminoglycans that were produced during chondrogenic activity, and which act to inhibit endochondral mineralization. Therefore, the results are consistent with the hypothesis that lead alters cartilage matrix, thereby disrupting endochondral bone growth primarily through its interference with chondrogenic, not osteogenic, activity.

### Publications

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

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## Disorders of Reproduction Among Female Veterinarians

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Program Area: *Disorders of Reproduction*  
Grant Number: *5 R03 OH02380-02*  
Start & End Dates: *05/01/87 - 04/30/89*  
Funding Level: *\$21,358 (\$42,535 Cum)*

### Importance to Occupational Safety and Health

This project has provided new information about the reproductive health and occupational exposures among a cohort of female veterinarians. The potential occupational exposures of veterinarians include many known or suspected reproductive health hazards, including anesthetic gases, antineoplastic drugs, ethylene oxide, hormones, ionizing radiation, and pesticides. The findings may have implications for a much larger number of women in other health and health-related occupations, and perhaps, for women employed in agriculture.

### Objectives

The objective of this study is to examine self-reported health and occupational data obtained from a cohort of female veterinarians in order to: (1) estimate risk of selected reproductive disorders; (2) describe occupational exposures associated with veterinary practice; (3) compare observed rates of reproductive disorders to relevant national natality statistics; and (4) conduct epidemiologic data analyses to identify associations between occupational exposures and selected reproductive outcomes.

### Methodology

Data were collected on the reproductive health and occupational exposures of the 2,997 female veterinarians who graduated from U.S. veterinary colleges in the period 1970-1980. The cohort was surveyed by a mailed, self-administered questionnaire instrument designed with input from NCHS, NIOSH, and NIEHS. For each respondent, the questionnaire elicited information on chronic

illness, injuries and accidents, reproduction, zoonotic disease, rabies exposure, employment, occupational exposures, and personal behaviors such as drug, alcohol, and tobacco use. A telephone follow-up of postal-survey non-respondents was also conducted. Cohort and nested case-control analyses focused on associations between specific reproductive outcomes and the self-reported occupational exposures.

### Significant Findings

1. The women comprising the cohort of female veterinarians selected for study were found exceptionally cooperative: postal survey results augmented by telephone follow-up of mail non-respondents achieved an overall response rate of 90.2%.
2. Nearly 3/4 of women veterinarians enter clinical practice immediately upon graduation from veterinary school. Among these women, approximately 3/4 engage in all-small-animal or mixed practices. More than 50% of the respondents reported job-related exposure to disinfectants, antibiotics, animal insecticides, formaldehyde, DES, non-DES hormones, halothane, non-halothane anesthetics, radiation, and solvents.
3. As with female veterinarians in general, the potential for pregnant female veterinarians to have contact with a wide variety of potential reproductive hazards is similarly quite high and, therefore, cause for concern.
4. As anticipated, the natality experience of the cohort was found notably different from that of the general population. Compared to U.S. white females, cohort members exhibit lower risk of all the adverse reproductive outcomes studied.
5. Risk of spontaneous abortion (SA) among female veterinarians was found to vary by the clinical practice type (CPT) reported at the time of conception, with all-large-animal, and in particular, all-equine practitioners exhibiting the highest absolute and relative risks. In CPT comparisons using unemployed women veterinarians as referents, confounder-adjusted relative risk estimates were found to be 1.5 (95% confidence interval (CI) = 0.5-4.3) and 2.1 (95% CI = 0.6-7.4), respectively.
6. No excess risk of SA was found associated with occupational exposure to disinfectants, halothane, non-halothane anesthetics, solvents, radiation, antibiotics, heavy metals, ethylene oxide, animal insecticides, DES, non-DES hormones, or formaldehyde. However, a slight increase in SA risk was found associated with occupational exposure to antineoplastics

(confounder-adjusted relative risk estimate = 1.14, 95% CI = 0.8-1.5).

7. Although based on sparse data, occupational exposure to halothane was found to increase the risk of small-for-gestational-age (SGA) birth on the order of 40 percent (confounder-adjusted relative risk estimate = 1.4, 95% CI = 0.6-3.2). The data were too sparse to address the question of SGA birth and clinical practice type.
8. Risk of pre-term delivery was found to vary by clinical practice type at the time of conception over a wide range, with all-large-animal and all-equine practitioners again exhibiting the highest absolute and relative risks. In comparisons using unemployed women veterinarians as referents, the confounder-adjusted relative risk estimate for all-equine practitioners was 28.8 (95% CI = 0.8(>100)).
9. Slight increases in risk of pre-term delivery were found associated with occupational exposure to disinfectants (confounder-adjusted relative risk estimate = 1.3, 95% CI = 0.8-2.2). No other agent-specific associations were seen.
10. In the nested case-control study of infertility that was conducted, modestly elevated odds ratios (ORs) were found to correspond with occupational exposure to antineoplastics (age-adjusted OR = 1.3, 95% CI = 0.9-2.0) and ethylene oxide (age-adjusted OR = 1.2, 95% CI = 0.7-2.1). Treating the number of hours worked per week as a surrogate measure of exposure intensity/frequency, confounder-adjusted relative risk estimates for antineoplastics increased monotonically from 1.1 among women veterinarians working <40 hours per week, to 1.3 among those working 40-49 hours per week, to 1.4 among those working >49 hours per week (trend P = 0.08). For ethylene oxide, confounder-adjusted relative risk estimates increased from 1.1 among those women working 40-49 hours per week to 1.7 among those working >49 hours per week (trend P = 0.10).
11. Although an uncontrolled observation, many of the women reporting a history of fertility problems were married to veterinarians, suggesting an area for further study.
12. One respondent reported accidental self-injection of a prostaglandin compound while 14-15 weeks pregnant, resulting in miscarriage. Although anecdotal in nature, this incident heightens awareness of needle sticks as reproductive hazards.

## Publications

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Moritz SA, Hueston WD, Wilkins JR III: Patterns of Ionizing Radiation Exposure Among Female Veterinarians. *JAVMA* 195:737-739, 1989

Crawford JM, Wilkins JR III, Steele LL, Hueston WD: Infertility and Occupational Exposures Among Female Veterinarians: A Nested Case-Control Study. *Am J Epidemiol* 130:835, 1989 (Abstract)

Steele LL, Wilkins JR III, Crawford JM, Gerken D, Hueston WD: Occupational Exposure to Reproductive Hazards Among Pregnant Female Veterinarians. *Am J Epidemiol* 130:835, 1989 (Abstract)

Gerken D, Wilkins JR III, Hueston WD, Steele LL, Crawford JM: Descriptive Analysis of Reproductive Health of Female Graduates from 1970-1980. *AWV Bulletin* 43:12, 1988

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## Menstrual Function in Nurses Exposed to Cancer Drugs

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Program Area: *Disorders of Reproduction*  
 Grant Number: *5 R03 OH02383-02*  
 Start & End Dates: *09/29/87 - 09/28/89*  
 Funding Level: *\$6,518 (\$29,442 Cum)*

### Importance to Occupational Safety and Health

The goal of this research was to investigate the effects on menstrual function associated with occupational exposure to antineoplastic drugs. The investigation provides additional information on the reliability of self-reported histories of menstruation and reproduction. In addition to assessing normal variations in menstrual cycles, the study provides

information on possible health effects in a cohort followed prospectively.

### Objectives

1. Assess the reliability of self-reported menstrual and reproductive histories in nurses exposed to antineoplastic drugs.
2. Assess patterns of ongoing occupational exposure to antineoplastic drugs and its effects on the menstrual cycle.
3. Assess the effect of difference in the use of protective equipment on menstrual cycles.

### Methodology

A national sample of 2,028 nurses who were members of the Oncology Nursing Society or the American Nurses Association agreed to participate in a follow-up study of health effects associated with work factors. These nurses were mailed a brief questionnaire requesting information on current employment status, antineoplastic drug and other occupational exposures, and use of protective equipment if they were currently handling antineoplastic drugs. Information on current menstrual cycles and general health status was obtained. In addition, a sub-sample of nurses was asked to answer menstrual history questions identical to those in the previous study so that test-retest reliability could be determined.

### Significant Findings

Survey participants in 1985-86 (n = 1893) were successfully contacted for this follow-up study. Response rate was 82% (n = 1550). There were 1,007 female subjects less than age 46 to use in the analyses of menstrual symptoms (mean age = 36.0 years). The sample was predominately married (68.4%) and caucasian (98.3%) and resided in 48 of the 50 states. Almost half of the subjects reported being employed in large community hospitals or research/medical centers (47.5%); however, ambulatory settings were also represented. Thirty-five percent of the sample (n = 356) reported currently handling antineoplastic drugs on a regular basis.

Reliability of menstrual and gynecological histories and information on exposure to antineoplastic drugs was assessed among a sub-sample of subjects who completed a second questionnaire. Test/retest reliability was high for recall of a history of irregular periods ( $\kappa = .723$ ), but recall of other menstrual characteristics was less reliable.

In 1986, an association was found between menstrual dysfunction and the current handling of antineoplastic drugs among subjects between ages 30 and 46. The prevalence odds ratio for this group was 1.6 when compared with subjects of the same age range with no previous or current handling of antineoplastic drugs. In 1988, the incidence of menstrual dysfunction was determined in the sample experiencing normal menstrual function in 1986. Nurses currently mixing and administering were 1.75 times more likely to report menstrual dysfunction when compared with controls; however, this difference was not statistically significant.

The use of protective equipment from 1985 to 1988 was compared using the McNemar test for paired data. Overall, the use of protective equipment increased. Consistent use of gloves increased from 72.8% to 84.2% when mixing antineoplastics, but consistent use of gowns while mixing only increased from 36.6% to 37.3%. Availability of vertical-flow hoods increased from 35% to 65%. Nurses reported an increase in the consistent use of gloves while administering antineoplastics (53% to 76%), while use of other protective equipment was rare. Nonusers of protective equipment were more likely to be employed in research centers or physicians' offices.

### Publications

Shortridge LA: Advances in the Assessment of the Effect of Environmental and Occupational Toxins on Reproduction. *Journal of Perinatal and Neonatal Nursing*, in press, 1989

Shortridge L, Valanis B, Lemasters G, Hertzberg V: Menstrual Cycles in Nurses Handling Antineoplastic Drugs. *American Journal of Epidemiology* 130:835, 1989 (Abstract)

Shortridge L: Assessment of Menstrual Variability in Working Populations. *Reproductive Toxicology* 2:171-76, 1988

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## Adverse Pregnancy Outcomes Among Cosmetologists

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Program Area: *Disorders of Reproduction*  
 Grant Number: 5 R03 OH02548-02  
 Start & End Dates: 09/29/87 - 03/31/90  
 Funding Level: \$21,675 (\$43,425 Cum)

### Importance to Occupational Safety and Health

Cosmetology entails two potential hazards to reproduction: chemical exposures and physical work demands such as prolonged standing. Chemical exposure through inhalation and dermal absorption is of concern since cosmetologists are in daily contact with a variety of cosmetic products such as hair shampoos, rinses, permanent wave solutions, hair dyes, hair relaxers and strengtheners, hair sprays, make-up, nail polish, detergents, antiseptics, and sterilizing solutions. Cosmetologists constitute a potentially high risk group with frequent and largely unmonitored chemical exposure. More than half a million U.S. women are employed in cosmetology, many of whom are of childbearing age. Epidemiologic evidence on adverse reproductive outcomes associated with chemical exposures in cosmetology is very limited, and this will be the first investigation of pregnancy outcomes in this occupational group.

### Objectives

The study will assess whether female employment in cosmetology around the time of pregnancy increases the risk of spontaneous abortion, pre-term delivery, or low birth weight. The frequency of adverse pregnancy outcomes among licensed cosmetologists who were working in cosmetology during their most recent pregnancy will be compared to that among licensed cosmetologists who worked in other occupations or as full-time homemakers.

### Methodology

Licensed cosmetologists in North Carolina (NC) were identified through the computerized

cosmetology license register, which includes both active and inactive cosmetologists. All cosmetologists meeting the following eligibility criteria were invited to participate: (1) female, (2) 22-36 years of age in 1988, (3) licensed in NC in April, 1988, and (4) residence in NC at the time of license renewal for the period 1986-1988. Thus, 8,356 eligible cosmetologists were identified. Data collection consisted of two self-administered mailed questionnaires. First, a two-page screening questionnaire was sent to 8,356 cosmetologists. Those with a single live birth or spontaneous abortion of less than 20 weeks gestational age between April 1983 and March 1988 were sent a longer questionnaire. More detailed data were collected on the outcome of the most recent pregnancy, work activities during pregnancy, and other potential risk factors. Stratified analyses and logistic regression modeling will be applied to assess the independent relationship between employment in cosmetology and adverse pregnancy outcomes.

### Significant Findings

Data collection is complete and data analysis has begun. No results are available yet.

### Publications

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

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## Physical Activity During Pregnancy and Birth Weight

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

### Importance to Occupational Safety and Health

Women of childbearing age represent an increasingly large proportion of the United States workforce, comprising 31.6% according to 1984 Bureau of Labor statistics. Increasing numbers of

pregnant women are continuing in their employment up until the time of delivery. Little is known concerning the risks and benefits of occupational activity on pregnancy outcome. Despite inadequate measures of physical activity employed, several epidemiologic studies of occupational activity and birth weight have shown an association between working outside of the home and decreased birth weight which was twice the magnitude of that observed among infants of mothers who smoked during pregnancy.

### Objectives

The aim of this research is to examine the relationship of occupational, leisure time, and household activity levels during pregnancy to birth weight. The study will determine the risks and benefits of physical activity in pregnant women. Types and patterns of activity are being assessed prospectively during each trimester of pregnancy and related to birth outcome.

### Methodology

Study participants consist of 300 women who will deliver at Magee-Womens Hospital in Pittsburgh. Subjects are being recruited from Magee-Womens Hospital obstetrics clinic and from private obstetricians' offices. The subjects are being recruited in a consecutive manner as they report for their prenatal care.

Data being collected include demographic characteristics, exposure history, behavioral characteristics (smoking, alcohol, and drug use) and a medical-reproductive history. An assessment is made of each woman's total daily physical activities. Occupational activity is assessed by an adapted version of the CDC-Behavioral Risk Factor Surveillance Form, which has been designed to address the key issues of physically demanding job tasks as well as the amount of hours spent sitting and standing still at work. A survey instrument developed by Dr. Andrea Kriska has been adapted to assess leisure time and household activities in the subjects.

Data are being collected regarding date of last menstrual period, ultrasound evaluations, and Dubowitz examinations in order to calculate gestational age. After delivery of the infant, birth weight is abstracted from medical records. Physical activity during working hours and leisure time will be the primary independent factors in the analysis; birth weight and gestational age are the dependent variables. Pearson correlation coefficients between activity and birth weight will be computed. Simple categorical analyses will be performed by dividing

physical activity levels into quintiles and examining mean birth weight and gestational age by these quintiles. Mean number of hours standing still and sitting will also be assessed according to birth weight and gestational age. A multiple regression analysis will evaluate whether physical activity during pregnancy is an independent predictor of birth weight and/or gestational age.

### Significant Findings

Sixty-one percent (184) of the total sample of 300 women have been recruited. The recruitment process will be completed by March of 1990. The results that can be reported to date are limited, as only 45 (15%) of the 300 total pregnancies have been completed.

Among the 45 women who have delivered their infants, 38% (17) were employed during their pregnancies. A total of four (9%) of these infants met the WHO criteria for LBW i.e., weight < 2500 grams. [The LBW rate in the United States in 1984 was 6.9%]. However, all four of the infants were also premature, i.e., < 37 weeks gestation. Two of the four women were employed during their pregnancy. Ten (22%) of the infants weighed between 2500-2999 grams. Among these women, 5 (50%) were employed outside of the home. One of these 10 infants was also premature. The remaining 31 infants (69%) were  $\geq$  3000 grams. Of this group, 10 (32%) of the women were employed outside the home. None of these infants were < 37 weeks of gestation. The prematurity rate was 11.1%. Two of the five women who delivered prematurely were employed. The median birth weight in working (N=17) vs. nonworking (N=28) women were 3080 g and 3280 g, respectively. Although this difference is not significant statistically with these small numbers, a trend appears to be emerging in the data, suggesting that working during pregnancy is associated with lower birth weight.

## Occupational Neuropathies Due to Industrial Chemicals

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Program Area: *Neurotoxic Disorders*  
Grant Number: *5 R01 OH00823-10*  
Start & End Dates: *01/01/86 - 12/31/89*  
Funding Level: *\$158,717 (\$1,169,713 Cum)*

### Importance to Occupational Safety and Health

This project is designed to study the mechanism(s) of joint neurotoxic action and develop specific biomarkers of neurotoxicity resulting from exposure to multiple neurotoxic chemicals, a situation that is frequently encountered in industry. These studies have shown that exposure to multiple chemicals leads to changes in their individual neurotoxicity resulting in: (1) potentiation of their neurotoxic actions, e.g., EPN and *n*-hexane, (2) synergism of a weak neurotoxicant, i.e., *n*-hexane or EPN by a non-neurotoxicant, i.e., MiBK, or (3) antagonism of a weak neurotoxicant, i.e., *n*-hexane by toluene. The results also suggest that accumulation of neurofilaments, the pathognomonic feature of *n*-hexane neurotoxicity, results from its oxidation to 2,5-hexanedione which leads to (1) decrease in Ca<sup>2+</sup>-calmodulin-dependent kinase phosphorylation of the neurofilament triplet proteins, (2) cross-linking of these proteins, and (3) diminishing of breakdown of cross-linked proteins.

### Objectives

The overall objective of this project is to investigate study the joint neurotoxic action of two groups of chemicals associated with neurologic dysfunction in humans: organophosphorus (i.e., EPN, TOCP) and aliphatic hexacarbons. The goal of these studies is to develop specific biomarkers by studying the target proteins in the nervous system and liver microsomal xenobiotic metabolizing enzymes.

### Methodology

The adult hen is the experimental animal since it is sensitive to neurotoxicity produced by both

classes of chemicals. Dermal exposure of EPN and inhalation exposure to hydrocarbon solvents were used since they are the major routes of occupational exposure both by industrial and agricultural workers. The pathogenesis of *n*-hexane neuropathy, characterized by accumulation of neurofilaments is being studied. Neurofilaments, triplet proteins from spinal cord, are isolated and analyzed using dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), immunoplotting, and kinase-mediated protein phosphorylation. Liver microsomal cytochrome P-450 isozymes, from control and treated hens, are isolated using column chromatography and characterized by SDS-PAGE and immunoblotting.

### Significant Findings

Early results in this project established that although organophosphorus compounds and *n*-hexane chemicals produce similar clinical features in the hen, they have distinct morphology and distribution of the neuropathologic lesions. Concurrent exposure to dermal EPN and MBK vapor resulted in potentiation of their neurotoxic action. Also, neurotoxicity of the weak neurotoxicants *n*-hexane was synergized by non-neurotoxicant methyl iso-butyl ketone (MiBK). Similarly, simultaneous dermal exposure to EPN and *n*-hexane and its metabolites resulted in additive or potentiating effects. The joint neurotoxic action of organophosphorus compounds and *n*-hexane may have resulted from the induction of hepatic cytochrome P-450. Also, *n*-hexane and its metabolites may have enhanced dermal absorption of EPN. Neurotoxicity resulting from simultaneous exposure to *n*-hexane and MiBK was characterized by cross-linking of the three neurofilament triplet proteins; 70 kDa, 160 kDa, and 220 kDa in the spinal cord. Ca<sub>2+</sub>-calmodulin-dependent kinase phosphorylation of these proteins was also diminished. Acute cholinergic and delayed neurotoxic effects of EPN were increased by simultaneous treatment with *n*-hexane and MiBK. Inhalation of MiBK or a mixture of MiBK and *n*-hexane induced liver microsomal cytochrome P-450 and increased the oxidation of EPN to EPN oxon. Two cytochrome P-450 isozymes (P-450 PB-A and PB-B) and cytochrome b<sub>5</sub> were purified to electrophoretic homogeneity from livers of phenobarbital-treated adult hens. Both isozymes have the apparent molecular weight of 54 kDa by SDS-PAGE. The antibodies raised against P-450, PB-A, and PB-B neither cross-reacted with each other nor with microsomal P-450s of rat, mice, cat, or catfish by immunoblotting. Also, four cytochrome P-450 isozymes ( $\beta$ -NFA,  $\beta$ -NFB,  $\beta$ NFC,

and  $\beta$ -NFD) were purified and characterized from  $\beta$ -naphthoflavone-treated adult hens. Hens exposed to toluene vapor (1,000 ppm) neither developed neurologic dysfunction nor neuropathologic lesions. Also concurrent exposure to toluene and *n*-hexane or MiBK did not produce neurotoxicity.

#### Publications

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

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

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

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

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

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

Abou-Donia MB, Lapadula DM, Campbell GA, Timmons PR: The Synergism of *n*-Hexane-Induced Neurotoxicity by Methyl Iso-butyl Ketone Following Subchronic (90 Days) Inhalation in Hens: Induction

of Hepatic Microsomal Cytochrome P-450. *Toxicol Appl Pharmacol* 81:1-16, 1985

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

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## Mechanisms of Occupational Neuropathies

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Program Area: *Neurotoxic Disorders*  
Grant Number: *5 R01 OH02003-03*  
Start & End Dates: *05/01/85 - 10/30/88*  
Funding Level: *\$198,511 (\$660,139 Cum)*

### Importance to Occupational Safety and Health

Determination of the mechanisms of neurotoxicity from occupational exposure to toxic chemicals will provide insight into the prevention and treatment of occupational neurotoxic disorders.

### Objectives

The overall goal of this project is to study the mechanism(s) of organophosphorus compound-induced delayed neurotoxicity (OPIDN) in a sensitive mammalian species, i.e., the cat, in comparison with the test animal to study OPIDN, i.e., the chicken.

### Methodology

The present studies into the mechanisms of OPIDN are carried out in the hen, the experimental animal for OPIDN, and the cat, a mammalian species that may be a better model for extrapolation to humans. Test chemicals used in these studies are the delayed neurotoxic organophosphorus compounds tri-*o*-cresyl phosphate (TOCP) and diisopropyl phosphorofluoridate (DFP). Parathion is used in some experiments as a non-delayed neurotoxic compound (negative control). CaM Kinase II,  $\alpha$ - and  $\beta$ -tubulin, MAP-2, and

neurofilament triplet proteins are isolated. *In vitro* phosphorylation of cytoskeletal proteins is performed using [ $\gamma$ - $^{32}$ P]ATP followed by SDS polyacrylamide gel electrophoresis (SDS-PAGE) and autoradiography. Identification of cytoskeletal proteins is carried out using one- and two-dimensional SDS-PAGE, peptide mapping, and immunoblotting. Quantification of protein content and  $^{32}$ P incorporation is performed with laser scanning densitometry.

### Significant Findings

Based on the results of this project and on previous studies, we propose the following mechanisms for OPIDN:

1. Delayed neurotoxic organophosphorus compounds phosphorylate a neurotoxic target protein, e.g., CaM Kinase II, resulting in conformational changes of the enzyme which increased its enzymatic activity.
2. Increased activity of CaM Kinase II enhances its autophosphorylation and leads to an increased CaM Kinase II-dependent phosphorylation of cytoskeletal elements, i.e., tubulin, MAP-2, and neurofilament triplet proteins.
3. Enhanced CaM Kinase II phosphorylation of cytoskeletal proteins leads to their loss of capacity to assemble into polymers; instead they aggregate into solid masses and/or undergo  $\text{Ca}^{2+}$ -activated proteolysis.
4. As a consequence, axonal transport of cytoskeletal protein is impaired which causes accumulation of mitochondria at the distal portion of the axon.
5. Mitochondria then break down and release their  $\text{Ca}^{2+}$  which promotes  $\text{Ca}^{2+}$ -dependent proteolysis and disrupts intracellular/extracellular ionic gradients. This leads to focal swelling followed by focal degeneration that spreads somatofugally to involve the entire distal axon.

### Publications

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

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Triplet Proteins Following a Single Oral Dose of Tri-o-Cresyl Phosphate. *Proc Nat Acad Sci* 83:6174-6178, 1986

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Carrington CD, Abou-Donia: Paraoxon Reversibility Inhibits Neurotoxic Esterase. *Toxicol Appl Pharmacol* 79:175-178, 1985

Patton SE, Lapadula DM, O'Callaghan JP, Miller DB, Abou-Donia MB: Changes in *In Vitro* Brain and Spinal Cord Protein Phosphorylation After a Single Oral Administration of Tri-O-Creysl Phosphate in Hens. *J Neurochem* 45:1567-1577, 1985

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## Peripheral Markers of Styrene Toxicity

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Program Area: *Neurotoxic Disorders*  
Grant Number: *1 R01 OH02629-01*  
Start & End Dates: *12/01/88 - 11/30/90*  
Funding Level: *\$152,175 (\$152,175 Cum)*

### Importance to Occupational Safety and Health

Adverse consequences of chemical toxicants are typically detected only after severity of health effects increases sufficiently to result in morbidity or mortality. There is a growing trend in occupational health research to develop and validate methods for early detection of biochemical changes caused by toxic workplace exposures. Biological monitoring is the term often used in this context. This project involves the application of several biological monitoring methods to detect responses to the industrial chemical styrene. The markers evaluated in this study are measured in peripheral blood cells. If these bio-markers are shown to be associated with extent of exposure, and are correlated with clinical symptoms, then these assays may be useful for monitoring occupational populations exposed to styrene and related chemicals. Ultimately, worker health surveillance programs should adopt relatively non-invasive methods to screen for early indicators of toxicity before debilitating exposure sequelae occur.

### Objectives

The overall objectives of this study are: (1) to explore the utility of bio-markers of neurotoxicity and chemical de-toxification potential in peripheral leukocytes of styrene-exposed workers; (2) to examine exposure-response relationships between levels of peripheral biochemical markers and

various exposure indicators; (3) to assess relationships between bio-marker levels and prevalence of central nervous system (CNS) symptoms; and (4) to examine exposure-response relationships for liver function parameters and styrene exposure.

The bio-markers used to assess neurotoxicity response are serotonin (5HT) uptake and monoamine oxidase B (MAO-B) in platelets, and sigma receptors in lymphocytes. Sigma receptor levels are determined from binding of three ligands: 3-H-spiperone, 3-H-di-o-tolylguanidine, and 3-H-haloperidol. Prior experimental evidence suggest that styrene may deplete dopamine in brain, thus resulting in a decrease of MAO-B which catabolizes dopamine. Serotonin uptake may be diminished as a result of styrene exposure, if predictions from prior animal experimental data apply to humans. Sigma receptors have been linked pharmacologically with various psychoses, and may be increased in response to styrene exposure. Two chemical detoxification enzyme systems, glutathione-S-transferase (GST) and epoxide hydrolase (EH), are being measured in peripheral lymphocytes. Benzo(a)pyrene oxide is used as the substrate in the GST and EH assays. Distortions in GST activity could result from glutathione depletion, a phenomenon that has been shown experimentally in styrene-treated rats. Activity of EH, which protects liver from many xenobiotic compounds, would be impaired, possibly in response to toxic metabolites of styrene, such as styrene oxide.

### Methodology

This study involves a repeated measures design in which blood and urine samples are obtained from styrene-exposed workers and a non-exposed reference group at two points in time. Exposed workers are volunteers from the reinforced plastics industry, and non-exposed workers are employed in other facilities that do not routinely use neurotoxic agents. The study sample consists of approximately 75 exposed workers and 25 non-exposed reference subjects. At each survey, worker exposures to styrene are determined from 8-hour time weighted average personal air monitoring. In addition, styrene doses are estimated from urine concentrations of mandelic and phenylglyoxylic acids, and from blood styrene levels. Venous blood samples are assayed for MAO-B, 5HT, sigma receptors, GST, and EH. The repeat measures design permits an evaluation of the stability of the biomarker data, and allows for assessment of change in biomarker results in relation to change in exposure. Liver function tests, including SGOT, SGPT, SGGT, bilirubin, and alkaline phosphatase,

are being performed for subjects at the second survey.

Additionally, a questionnaire eliciting demographic data, information on smoking and alcohol consumption, hobbies potentially involving exposures to neurotoxicants, prior work experience, medical history, and symptoms associated with CNS effects (e.g., feelings of drunkenness at work) is administered to all subjects at the initial survey. The data from this questionnaire include information on potential confounders (e.g., alcohol use), and relevant health outcomes (i.e., CNS symptoms). The symptom data will be used in a case-control analysis comparing exposures and biomarker data between subjects reporting excessive frequencies of symptoms and worker controls.

### Significant Findings

Data collection for the repeat surveys is nearly complete. Assays for styrene exposure air concentrations, sigma receptors, MAO-B, 5HT, GST, EH, and blood styrene have been completed for approximately 75 percent of subjects. Urine samples have been frozen, and will be assayed for mandelic and phenylglyoxylic acids when data collection is completed. Data analysis will be performed during the remainder of the funding period.

### Publications

Checkoway H, Costa LG, Coccini T, Rappaport SM, Manzo L: Monitoring Styrene Neurotoxicity with 3-H-Spiperone Binding in Lymphocytes. Proceedings of the VII International Symposium on Epidemiology in Occupational Health, Amsterdam: Elsevier, in press, 1990

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## Neurologic Effects of Solvents in Older Adults

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Program Area: *Neurotoxic Disorders*  
Grant Number: *1 R01 OH02683-01*  
Start & End Dates: *09/30/89 - 09/29/91*  
Funding Level: *\$230,717 (\$230,717 Cum)*

### Importance to Occupational Safety and Health

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

### Objectives

The study will address 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. Secondly, are there intergroup differences among selected non-neurologic areas of function?

#### Methodology

The study will use a cross-sectional design to examine neurologic function (subjective, neurosensory, neuropsychological, and psychiatric parameters) among retired painters, in comparison to a similarly examined control group. The control group will consist 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 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 will also be examined as outcomes of secondary interest.

#### Significant Findings

Data collection will begin soon. Identification of potential subjects, as well as final preparation of test instruments and protocols, are in progress.

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### ***In Vitro* Glial Responses to Halothane Metabolite, TFA**

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

#### Importance to Occupational Safety and Health

The results indicate that TFA affects glycoprotein synthesis by C6 glioma cells. This is consistent with the notion that anesthetics modify the target cell membrane. This finding could further the understanding of mechanisms of action of anesthetics, thereby aiding in the detection and prevention of occupational hazards associated with the use of halogenated alkanes and alkenes.

#### Objectives

The long-term objective for the proposed research is to elucidate the mechanism by which chronic exposure to very low concentrations of inhalant anesthetics leads to pathology of neuronal development. The specific aims for the current experiments are to determine the impact of trifluoroacetic acid (TFA), the principal oxidative metabolite of halothane, on rates of synthesis of DNA, proteins, glycoproteins, and fatty acids as well as the proliferative potential of cultured C6 glioma cells.

#### Methodology

Cell culture and TFA treatment: C6 glioma cells obtained from ATCC (Bethesda, MD) were maintained as a monolayer in RPMI 1640 medium supplemented with 5% fetal bovine serum and antibiotics in a humidified CO<sub>2</sub> incubator at 37°C.

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis: After exposure to 10 mM TFA for 24 h, C6 cells ( $2 \times 10^7$ ) were labeled with 50  $\mu$ Ci of D-[<sup>3</sup>H] mannose in 10 ml of glucose-free 1640 Medium for 2 h. The cells were washed with Ca<sup>+2</sup>, Mg<sup>+2</sup>-free phosphate buffered saline (PBS), four times freeze-thawed, and centrifuged at high speed for 10 min. The pellet was mixed with an equal volume of sample buffer (10% glycerol, 5% 2-mercaptoethanol, 30% SDS, 0.75% Tris and trace of bromophenol blue) and denatured by boiling at 100°C for 3 min. Aliquots of samples were added to a 7.5% slab SDS polyacrylamide gel. After running for 5 h at 150 V, the gels were fixed with a solution that contained 10% acetic acid and 45% methanol for 30 min; soaked in Fluoro-enhance autoradiography enhancer; dried on a Bio-Rad gel dryer; covered with Kodak X-Omat AR films; and exposed for 5 wk at -70°C. The densities of polypeptide bands were analyzed with a CS-9000 dual wave length Flying Spot scanner (Shimadzu Corp., Japan).

Cell agglutination assay: C6 cells were suspended in PBS at a concentration of  $5 \times 10^6$  cells/ml at 4°C. A 1.2 ml aliquot of the suspended cells was added to each cuvette, followed by the addition of Ricinus communis agglutinin (0, 25, 50  $\mu$ g). The contents were mixed rapidly by 4 consecutive inversions. Cuvettes were placed immediately in the chamber of a Gilford Response II spectrophotometer to measure the rate of change of absorbance at 546 nm.

### **Significant Findings**

The treatment of C6 cells with TFA resulted in accelerated ricinus communis agglutinin induced agglutination. SDS-polyacrylamide gel electrophoresis and autoradiography data showed that TFA inhibited significantly the glycosylation of cell membrane at Mr 92,500. In agreement with the previous finding, the results reveal further that TFA affects synthesis of glycoproteins in cell membranes, which may associate with the harmful effects of TFA on mammalian cells.

### **Publication**

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

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## The Effects of Impulse Noise on the Auditory System

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Program Area: *Noise-Induced Hearing Loss*  
Grant Number: 7 R01 OH01152-09  
Start & End Dates: 09/29/86 - 09/28/90  
Funding Level: \$174,548 (\$1,106,714 Cum)

### Importance to Occupational Safety and Health

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

### Objectives

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

### Methodology

Several mechanical or electrical-mechanical devices are used to produce realistic noise impacts. Hearing is tested, the animal is exposed to impulse/impact noise, and its hearing is tested for the following forty days. Routine data collection

consists of measurements of hearing sensitivity, auditory discrimination, and cochlear histology. More detailed studies of certain experimental groups will include scanning E.M., as well as more discriminating psychoacoustic measures of hearing.

### Significant Findings

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

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## Functional Correlates of Cochlear Injury

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Program Area: *Noise-Induced Hearing Loss*

Grant Number: *5 R01 OH02128-05*

Start & End Dates: *09/01/84 - 02/28/90*

Funding Level: *\$151,063 (\$630,167 Cum)*

### Importance to Occupational Safety and Health

The laboratory studies of noise-induced hearing loss in animal models and the relation with cochlear pathology directly address the long-term research goals described in the NIOSH prevention document. They will help to establish damage-risk criteria for human noise exposure, delineate the mechanisms of noise-induced hearing loss, determine the role of degenerative and recuperative processes, and help 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.

Field studies of hearing of industrial workers will address the objective of collecting data from workers exposed to occupational noise as a baseline for comparing the hearing of groups of workers exposed to noise. The field studies will also help determine the role of non-occupational noise exposure on hearing levels of industrial workers.

### 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 are being made from the ear canals of all subjects. Finally, field studies in industrial workers are being conducted to determine the effect of non-occupational noise

exposure on hearing levels of individuals exposed to moderate to high levels of noise at work.

### Methodology

Hearing thresholds are obtained by behavioral methods in chinchillas before, during, and after noise exposure; the ears of all animals are then prepared for microscopic evaluation of the cochlea. Acoustic measures are made with small probe microphones positioned in the ear canal of the unanesthetized animal. Industrial surveys are made by audiometric database analysis of thresholds obtained as part of the company-wide hearing conservation programs.

### Significant Findings

Some of the findings of the project include:

1. Asymptotic threshold shifts appear to set an upper bound on permanent threshold shifts. Animals exposed continuously for periods up to 6 years have no more hearing loss during the sixth year of exposure than they had on the second day of the exposure.
2. Interrupting an exposure with rest is protective. Exposures with quiet periods interspersed produce less cochlear damage and less hearing loss than equal-energy continuous exposures.
3. Under some schedules of exposure, hearing sensitivity recovers even though the exposure continues. That is, some of the sensory elements of the inner ear can somehow "toughen" themselves against further insult by noise.
4. 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.
5. Chinchillas raised in a quiet environment for periods of up to 19 years show anatomical signs of age-related hearing loss (prebycusis), 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 suggests that much of what is typically called presbycusis in humans is caused by environmental factors, principally noise exposure.
6. In field studies of industrial workers, non-occupational noise exposure, particularly hunting and target shooting, are significant causes of hearing loss outside the workplace.

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## Hearing Hazard Associated with Industrial Noise Exposure

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Program Area: *Noise-Induced Hearing Loss*  
Grant Number: *5 R01 OH02317-05*  
Start & End Dates: *08/01/87 - 07/31/90*  
Funding Level: *\$192,891 (\$895,930 Cum)*

## Importance to Occupational Safety and Health

Many industrial noise environments are characterized by high levels of impact noise that are superimposed on a continuous background noise thus producing a very complex temporal signal. The limited demographic data and an increasing body of experimental data show that many of these "complex noise" environments pose an unusually high risk of hearing loss to the repeatedly exposed individual. The need exists to develop metrics which can be extracted from such "complex noise" environments and used to objectively estimate the hazards that such environments pose to hearing. Our research efforts are directed toward such a goal. Our experimental approach will yield a generalized methodology that can be used to model and evaluate all forms of industrial noise environments and holds the promise for producing metrics that can be incorporated into a new generation of measurement equipment and used to gauge the hazards posed by virtually any industrial noise environment.

## Objectives

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

## Methodology

An approach to digital noise generation has been developed which is capable of producing noise whose statistical properties and amplitude spectrum are under experimental control. The basic idea is

that the desired noise is designed in the frequency domain by manipulations of the phase spectrum. In essence, once an amplitude spectrum is chosen, phase spectrum manipulations can produce peaks in a continuous noise which derive their energy from any selected portions of the amplitude spectrum. Preliminary results indicate that entire families of noises having the same spectrum but continually varying statistical properties can be created. Noise environments similar to bottling, stamping, punch-press 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 spectral analysis and frequency domain kurtosis procedures are being explored as methods for extracting quantitative information from the non-Gaussian component of the noise. The animal experiments being conducted use a standard paradigm.

Chinchilla are being exposed for five continuous days to various non-Gaussian noise paradigms. Hearing thresholds are obtained prior to exposure and at regular intervals following exposure using brainstem evoked potentials. Sensory cell populations are obtained from each animal and relations between noise parameters, audiometry, and histology are derived.

### Significant Findings

Using combinations of impact and continuous noise whose exposure conditions are balanced to maintain equal energies, we have shown a clear exacerbation of hearing loss (audiometric and histological indices). This additional loss was dependent upon the total energies, peak impulse levels, and frequencies of the two classes of noise. When the total energy of the exposure is increased by 1.5 to 2.0 dB under exposure conditions that contain high level impact noise (119 dB peak SPL), differences of up to 20 dB in permanent threshold shifts (PTS) can be measured. These experiments clearly demonstrate that the measurement of an rms level of a highly non-Gaussian noise can severely underestimate the hazard to hearing. A second series of exposures using very low levels (90 dB SPL) of synthesized noise whose kurtosis ( $\beta$ ) is varied from 3 (Gaussian noise) to 189 (highly non-Gaussian noise) is currently in progress. Both the  $\beta = 3$  and the  $\beta = 189$ , 90 dB SPL exposures produced no statistically significant differences in asymptotic threshold shift (ATS) at the 2 and 8 kHz test frequency where ATS levels of 50 to 60 dB were measured. At the .5 kHz test frequency, the region in the vicinity of the spectral peak of the noise, there was a statistically significant 10 dB

increase in ATS for the  $\beta = 189$  group. For the high  $\beta$  group ( $N = 10$ ), there were 12-20 dB statistically significant (t-test) higher levels of PTS at the frequencies 4, 8, 11.2, and 16 kHz, while at .5, 1, and 2 kHz, there were no statistical differences between the  $\beta = 3$  and  $\beta = 189$  exposures. The hair cell losses, on the other hand, show over 30% OHC loss at 250 Hz for the higher  $\beta$  group and little loss for the  $\beta = 3$  group, a result that might be anticipated from the low frequency ATS results but not on the basis of the PTS data. More puzzling is the high frequency PTS for the  $\beta = 189$  group in the presence of no statistically significant difference in the OHC loss at the high frequencies among the  $\beta = 3$  and  $\beta = 189$  groups.

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## Effect of Industrial Work-Related Variables on Achieved Hearing Protector Attenuation

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Program Area: *Noise-Induced Hearing Loss*

Grant Number: *5 R01 OH02540-02*

Start & End Dates: *05/16/88 - 08/15/90*

Funding Level: *\$55,757 (\$107,502 Cum)*

## Importance to Occupational Safety and Health

For the worker exposed to hazardous levels of industrial noise, personal hearing protection devices (HPDs) are commonly used to protect against noise-induced hearing loss. It is estimated that over nine million American workers are exposed to daily average occupational noise levels above the 85 dBA time weighted average level at which OSHA requires HPDs to be supplied. The success of many industrial hearing conservation programs is dependent upon the performance of HPDs. Part of the HPD selection process entails a determination of the adequacy of the HPD for the particular offending noise problem. However, the practical industrial need is to have an accurate and reasonable estimate of the attenuation to be reliably obtained under workplace conditions. This research project is aimed at determining the effects of various work-related influences on hearing protector attenuation, with the objective of providing empirical data which reflect workplace performance, not optimal laboratory performance, of the devices. The results will shed light on the effectiveness of different HPDs under dynamic work conditions and over long wearing periods.

## Objectives

This two-year project entailed a laboratory attenuation study during the first year, and in the second year, a determination of on-the-job attenuation for industrial subjects has been undertaken. As a secondary initiative, user HPD comfort and acceptability data were obtained in the laboratory study and are again being obtained in-field. The fundamental objective of the laboratory simulation study was to determine if several "real-world" influences and different HPD fitting procedures could be reproduced in the confines of the laboratory and the magnitude of their effect on spectral attenuation loss with several common HPDs measured. The same HPDs as investigated in the laboratory study are now being used in-field, so that comparisons on common devices can be performed. In essence, the in-field study will serve as a validity check on the laboratory results to ascertain if workplace influences can be modeled in the laboratory to yield an accurate assessment of the device's protection performance that will be provided in the industrial setting.

## Methodology

The first-year laboratory study, a complete factorial experimental design was applied to assess the independent variables of HPD-type (pre molded

multi-flange earplug, user-molded foam earplug, foam cushion earmuff, and earmuff over foam earplug combination), movement activity, wearing time, and HPD fitting procedure on the dependent measures of attenuation in dB and self-report ratings. To provide a comparison against the usual laboratory test conditions of a seated, motionless subject wearing properly-fit HPDs for a short testing period, this study presented the potential real-world effectors of movement activity, subject fitting of the device, and prolonged wearing periods. All attenuation measurements were obtained in a sound field using Békésy computer-controlled audiometry, with occluded (HPD on) and unoccluded (open ear) thresholds determined at nine 1/3 octave test bands centered at 125 to 8000 Hz. Subjects consisted of 40 normal hearing, non-users of HPDs. Each subject attended four experimental sessions following screening and was assigned one HPD. In the first two sessions, subjects initially fit the HPD according to a "subject-fit" condition in which only manufacturer's package instructions were presented. In the last two sessions, subjects initially fit the HPD according to a "trained-fit" condition to achieve proper fit. In both fitting conditions, subjects ultimately fitted the devices on themselves, after which no further protector adjustments were allowed. After the initial fit of the device, attenuation was measured. Then subjects proceeded through a two-hour wearing period in which attenuation measurements were obtained after one hour and again after two hours. The wearing periods consisted of either highly kinematic work activity using a BTE Work Simulator or vigorous temporomandibular movement.

For the second-year study, actual industrial workers are being supplied with pre-selected HPDs to use while working. Workers will initially receive the HPDs with only the manufacturer's instructions as a guide to use. Following this, workers will use the HPDs for one month, during which on three occasions they will be pulled (unannounced) from their work at random intervals and attenuation-tested. At the end of this month, workers will receive more detailed training on proper fitting through an interactive session with the experimenter and will again return to the workplace to use the devices for a second month. Attenuation tests will again be conducted, unannounced, at similar intervals to those used during the first month. Thus, actual industrial protection levels will be obtained in this study. Furthermore, the effects of training for proper HPD fitting on long-term attenuation achieved in-field can be ascertained.

### Significant Findings

Subject-fit practices resulted in significantly lower protection levels than trained-fit, ranging from 4 to 14 dB at 1000 Hz and below for the pre-molded earplug, foam earplug, and muff/plug combination. The muff alone was significantly more resilient to differences in fitting procedures on attenuation than were the plugs. Both types of movement activities caused a significant reduction in frequency-specific attenuation over time for several, but not all devices. Up to a 6 dB reduction occurred for the premolded plug, muff, and muff/plug combination over the two-hour wearing period. However, the muff's loss in attenuation appeared to primarily be a function of slippage during work-related activity, not due to temporomandibular effects. The compliant foam earplug was largely insensitive to either type of movement effect, but it did benefit more than the other devices from the use of proper training to achieve a quality fit. These results indicate that for some highly kinematic situations, certain compliant HPDs may be preferred over others because of their tendency to remain stable in the face of vigorous movement. Also, some protectors, such as the premolded plug and muff investigated in this study, may require readjustment and/or re-fitting during use on the job. Workers should be aware of this fact and make the necessary adjustments, or it is entirely possible that protection will decrease over time, perhaps unbeknownst to the affected worker.

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

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Program Area: *Noise-Induced Hearing Loss*  
Grant Number: *1 R03 OH02671-01*  
Start & End Dates: *09/30/89 - 09/29/91*  
Funding Level: *\$18,246 (\$18,246 Cum)*

### Importance to Occupational Safety and Health

Vocational education laboratories such as Trade and Industrial Education, Industrial Arts Education, and Agricultural Education are equipped with tools and machinery which duplicate those used in the industry for which students are being prepared to enter.

The majority of vocational educators do not recognize the risk which noise poses to their students or themselves. Teachers lack basic information about the exposure levels they and their students experience in their instructional laboratories. In order to fill this informational vacuum and to prevent risk from noise exposure to vocational education students and instructors, the following objectives will be addressed.

### Objectives

1. To survey and develop an inventory of the power tools and equipment found in selected vocational education laboratories in Maricopa and Pima Counties, Arizona.
2. To measure the noise level in dB(A) of common power tools and equipment used in selected vocational education laboratories in Maricopa and Pima counties, Arizona.
3. To document the characteristics of the selected facilities which could have impact on noise levels.

4. To measure student and teacher percent dose for daily and 40 hour equivalent values, based on 3 and 5 dB exchange rates, in each facilities environment.
5. To disseminate findings and recommendations to vocational educators and administrators of vocational education programs by all available means.

### Methodology

This study will be conducted as descriptive research with survey data collected on-site by researchers. The accessible population 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 their programs in 1987 in Arizona.

The target population will include secondary students enrolled in Vocational Agriculture, Trade and Industrial Education, and Industrial Arts in Pima and Maricopa Counties where welding is specified as a part of the curriculum or the major emphasis of the course. Pima and Maricopa Counties contain 75% of the population of the state of Arizona.

From the 54 programs in Pima and Maricopa Counties offering welding, a proportional stratified random sample consisting of 50% of the programs (27) will be assigned to strata based upon type of facility. All 54 programs in Maricopa and Pima Counties will be surveyed by mailed questionnaire to determine the type of construction and acoustical treatments of the facility. The 27 selected programs will be assigned proportionally to the appropriate facility type.

Four students and the teacher will be randomly assigned to wear a dosimeter and data storage unit. Random assignment of students to dosimeters will reduce variability among students in welding and grinding techniques.

Data collected will be reported as frequencies, means, and modes. Data collected will be daily and 40-hour equivalent values, based upon 3 and 5 dB exchange rates, for teachers and students. Correlations will be calculated between the above factors and the strata of facility type.

The acoustical characteristics of each facility will be evaluated by determining reverberation time (RT60). Dimensional measurements will be taken and materials of construction will be noted. Any noise attenuating features will be noted such as insulation, ceiling tile, etc..

**Significant Findings**

This project is currently in the process of purchasing equipment and identifying the accessible populations in Pima and Maricopa Counties, Arizona.

## Immunotoxicology of Phenols on Epidermal Immune Cells

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Program Area: *Dermatological Conditions*  
Grant Number: 5 R01 OH02091-05  
Start & End Dates: 08/01/87 - 07/31/90  
Funding Level: \$149,081 (\$427,702 Cum)

### Importance to Occupational Safety and Health

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

Since the 1930's it has been well documented that antioxidants like monobenzene or paraterter 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 monobenzene, paraterter 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- $\gamma$  (IFN- $\gamma$ ) and IL-1. A third cytokine,  $\alpha$ -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 susceptible 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  $\alpha$ -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.  $\alpha$ -MSH is a potent melanotropic stimulant and an immune suppressant.  $\alpha$ -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- $\gamma$  and ICAM are under study.

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

#### Publications

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## Biological Monitoring for Exposure to Coal Tar

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Program Area: *Dermatological Conditions*  
Grant Number: *1 R01 OH02622-01*  
Start & End Dates: *01/01/89 - 12/31/90*  
Funding Level: *\$209,850 (\$209,850 Cum)*

### Importance to Occupational Safety and Health

A major goal of biological monitoring for exposure to genotoxic agents is to identify occupations as well as individuals at elevated risk for cancer development. Methods for the detection of carcinogen-DNA and protein adducts have been developed. These methods require the collection of blood or tissue samples and are not practical for routine occupational monitoring. In this proposal, methods will be developed for the determination of exposure to benzo(a)pyrene (BP) by measurement of BP and its metabolites in urine. Urine is much more easily collected than blood, and 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 urinary excretion. An immunoassay for measurement of BP and its metabolites in urine will be developed utilizing monoclonal antibodies recognizing these compounds. This new assay will be validated in a model population, crude coal tar treated psoriasis patients and controls. Blood and urine will be collected from patients and controls. Exposure to BP will be measured by a panel of previously developed assays including quantitation of white blood cell DNA adducts by immunoassay and <sup>32</sup>P postlabeling, measurement of albumin adducts by immunoassay and measurement of serum antibodies to BP-DNA adducts by immunoassay. Urines will be analyzed for excreted mutagens with the Salmonella typhimurium assay as well as with the new immunoassay to be developed in this proposal.

The levels of different biological markers will be correlated with exposure.

### Methodology

To develop an immunoassay for the measurement of BP and its metabolites in urine, monoclonal antibodies will be developed from animals immunized with BP covalently coupled to carrier protein. These antibodies will be characterized in terms of sensitivity and specificity by competitive enzyme-linked immunosorbent assay (ELISA). An ELISA will be developed for the sensitive detection of BP and a number of its metabolites in urine. To validate the ELISA, mice will be treated with radiolabeled BP and urine collected. Metabolites will be measured by the ELISA and values compared to those determined by radioactivity.

Blood and urine will be collected from 40-50 crude coal tar treated psoriasis patients and controls. Blood will be separated into plasma, white blood cell, and red blood cell fractions and frozen. DNA will be isolated from the white cells and adducts determined by ELISA utilizing previously developed antibodies against BP diol epoxide modified DNA. These antibodies recognize a number of structurally related PAH diol epoxide adducts and thus provide a general marker of exposure to this class of chemicals. Total hydrophobic adducts will be quantitated with the <sup>32</sup>P postlabeling assay. BP protein adducts will be 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, mutagens in urine will be determined with the Salmonella typhimurium mutagenesis assay. Results from the different biological assays will be correlated with exposure.

### 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 enzyme-linked immunosorbent assay (ELISA). The ELISA has a 50% inhibition of antibody binding at 4pmole of BP/well. There is also significant cross-reactivity with a number of BP metabolites including 1-, 3-, 4-, 5-, and 11-hydroxy-BP, 7,8- and 9,10-BP diols and 7,8,9,10-BP tetrol. Several other PAHs, including pyrene,

1-OH-pyrene, 1-aminopyrene and 1-nitropyrene, cross-react with the antibody. An ELISA was developed for the sensitive detection of BP and a number of its metabolites in urine. To validate the ELISA, mice were treated with radiolabeled BP and urine collected. After treatment with beta glucuronidase and aryl sulfatase, metabolites were isolated by several different chromatography procedures. These included extraction with ethyl acetate, chromatography on Sep-pak C18 cartridges, chromatography on an Amberlight XAD2 column and immunoaffinity chromatography with the monoclonal antibodies. Sep-pak and immunoaffinity chromatography gave the highest recovery of metabolites. Isolated metabolites were counted for radioactivity and analyzed by competitive ELISA. The values by ELISA, determined with a standard curve of BP, were about one-third those determined by radioactivity. Since unmetabolized BP is not excreted in the urine, it is not accurate to use it as the standard. We have begun to analyze the mouse urine by HPLC to determine which metabolites are present. However, we will utilize BP in the standard curve for the human samples since it will not be possible to identify metabolites present in human urine. Thus, the assay will provide a relative measure of metabolites present.

#### Publications

Gomes M, Santella RM: Immunologic Methods for the Detection of Benzo(a)pyrene Metabolites in Urine. Chemical Research in Toxicology, accepted, 1990

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### Mechanisms of Cytotoxicity by Chlorodinitrobenzene, A Potent Sensitizer

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Program Area: *Dermatological Conditions*  
Grant Number: 5 R03 OH02433-02  
Start & End Dates: 09/28/87 - 09/28/89  
Funding Level: \$26,700 (\$53,190 Cum)

#### Importance to Occupational Safety and Health

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1-chloro-2,4-dinitrobenzene (CDNB), a halogenated nitrobenzene derivative of hydrocarbon, is a potent skin sensitizer causing severe allergic contact dermatitis, and thus is a documented occupational hazard. The total glutathione (GSH) content is important for cellular recovery from CDNB-mediated cytoskeletal injuries, and depletion of cellular glutathione alone cannot account for microtubule (MT) disassembly and microfilament (MF) disorganization observed in CDNB-treated cells. Maintenance of an appropriate level of GSH is important in protecting the cells from cytoskeletal injuries induced by CDNB.

The sensitizing capacity of halogenated nitrobenzenes towards guinea pigs appeared to correlate well with their ability to induce cytoskeletal perturbations. These results suggest that an *in vitro* assay based on cytoskeletal perturbations may be developed for screening other potential halogenated nitrobenzene sensitizers.

#### Objectives

Previous studies from this laboratory have shown that CDNB induces MT disassembly in mouse 3T3 cells. Blocking of certain -SH groups of tubulin, the principal protein component of MT, with -SH reagents inhibits tubulin polymerization *in vitro*. Since GSH is the predominant non-protein thiol in the cells, it is reasonable to expect that GSH is involved in the dynamics of MT state. Furthermore, GSH is crucial for cellular defense against insults by toxic electrophiles by forming appropriate conjugates with the toxicants through the action of glutathion-S-transferase (GST). However, the mechanisms by which CDNB induces cytoskeletal perturbation and its relationship to the ultimate cellular injury are not clear. Therefore, the objectives of the project are: (1) to determine whether CDNB acts directly on the cytoskeleton by binding to tubulin/MT in the cells resulting in MT disassembly; (2) to investigate the role of the total cellular GSH content, which can be either increased or decreased by the use of specific agents, in modulating the dynamics of MT assembly and disassembly and MF distribution during CDNB exposure; (3) to quantitate the amount of cellular free vs. polymerized tubulin and actin (the major protein of MF) by developing an ELISA assay for each protein. Studies on the relationship between

the cellular GSH contents and the dynamic changes in the cytoskeleton of human fibroblasts and human keratinocytes may lead to a better understanding of the mechanisms of induction of allergic contact dermatitis caused by CDNB and other related halogenated nitro derivatives of hydrocarbon.

### Methodology

Swiss mouse 3T3 fibroblasts, human skin fibroblasts, and human keratinocytes are used in these studies. Total cellular GSH is measured by Tietze assay, and cellular non-protein thiols are measured by HPLC. Cytoskeletal elements, MT and MF, are monitored by fluorescence microscopy and quantitation of tubulin and actin is done by ELISA. Buthione sulfoximine (BSO) and cyclohexeneone are used to decrease cellular GSH, whereas GSH monoethyl ester is used to increase cellular GSH.

### Significant Findings

Exposure of 3T3 cells to micromolar doses of CDNB, a substrate for GST, resulted in a rapid depletion of total cellular GSH accompanied by disassembly of MT as visualized by fluorescence microscopy. However, prolonged incubation resulted in cellular recovery from CDNB insult as evidenced by a steady rise in total cellular GSH and reassembly of MT to their normal distribution. To evaluate the role of total cellular GSH in modulating the CDNB-induced cytoskeletal perturbation, we used CDNB or/and BSO, an effective irreversible inhibitor of glutathione synthesis, to manipulate cellular glutathione levels. BSO increased the extent of cellular GSH depletion and MT disassembly of 3T3 cells over the level achieved by CDNB treatment alone. Furthermore, BSO also prevented the partial restoration of cellular glutathione content and MT reassembly that normally occurred in 3T3 cells after CDNB treatment. Exposure of 3T3 cells to 2-cyclohexene-1-one (CHX), which depletes free GSH by conjugation, resulted in a complete depletion of total cellular GSH content without altering the MT organization. Exposure of 3T3 cells to CDNB and GSH monoethyl ester, a cellular GSH delivery system, resulted in a large increase in cellular GSH content and MT disassembly induced by CDNB did not occur.

The sensitizing capacity of several halogenated nitrobenzenes has been tested in guinea pigs and later reproduced in humans. Exposure of 3T3 cells, human skin fibroblasts, and human keratinocytes for 3 hrs to halogenated nitrobenzenes, known to induce allergic contact dermatitis in guinea pigs,

resulted in a complete disassembly of MT. In sharp contrast, exposing cells for 3 hrs to halogenated nitrobenzene derivatives, which do not sensitize guinea pigs, had no discernible effect on the organization of MT.

### Publications

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## Mechanisms of Cytoskeletal Injury by Nickel Compounds

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Program Area: *Dermatologic Conditions*  
Grant Number: *1 R03 OH02655-01*  
Start & End Dates: *06/01/89 - 05/31/91*  
Funding Level: *\$25,895 (\$25,895 Cum)*

### Importance to Occupational Safety and Health

Nickel (Ni) is a well documented respiratory tract carcinogen among nickel refinery workers involved in high-exposure operations such as grinding, calcining, sintering, and leaching. Evidence from 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 controls. Many cases of severe acute and even fatal toxicity have also been reported following nickel carbonyl exposure. Furthermore, nickel 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. In this project, we will investigate the possible role of the cytoskeleton

in mediating cellular injuries by Ni compounds. The findings of this project may lead to an effective diagnostic tool in detecting Ni insults among workers at risk by examining the early manifestation of the dynamic changes in cytoskeleton via cytologic study.

### Objectives

The goal of this project is to elucidate the mechanisms by which Ni-induced cytoskeletal perturbation occurs in cultured 3T3 cells exposed to Ni, and its relationship to cell injury and possibly carcinogenesis. Effect of Ni on the *in vitro* polymerization of purified microtubule proteins containing tubulin and microtubule associated proteins (MAPs) will be investigated. Since MAPs play an important role in the polymerization and stabilization of microtubules, phosphorylation state and distribution of MAPs and their isoelectric variants will also be examined. With growing evidence of physical linkage between organelles and the cytoskeleton, Ni induced microtubule change may also result in a redistribution and possible damage in the normal function of cytoplasmic organelles such as mitochondria, the Golgi apparatus, ER, etc. Alteration in the function of vital organelles such as the mitochondria may lead to an imbalance of nucleotide pools which may contribute to the observed chromosomal damages observed in cells exposed to Ni. These issues will be investigated.

### Methodology

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

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

To investigate the possible redistribution of organelles induced by Ni, vital stains are used. DiOC<sub>6</sub>, a cyanine dye, selectively stains mitochondria at low doses and ER at higher doses. The Golgi apparatus can be visualized by

C<sub>6</sub>-NBD-ceramide label. Stained 3T3 cells will be examined under a fluorescence microscope.

For nucleotide pool analysis, the total cellular acid-soluble nucleotides of 3T3 cells are extracted with ice-cold TCA and analyzed by a Waters high pressure liquid chromatography (HPLC) on Whatman's Partisil-10 SAX ion exchange columns.

### Significant Findings

Ni<sup>2+</sup> was found to have a stimulatory effect on the rate of tubulin polymerization at concentrations ranging from 0.01 mM to 2.0 mM; this stimulatory effect seemed to peak at 2.0 mM. However, at Ni<sup>2+</sup> concentrations higher than 2.0 mM (up to 5.0 mM tested), Ni<sup>2+</sup> had an inhibitory effect on the rate of tubulin polymerization. These results agreed well with our immunofluorescence study using 3T3 cells in which 2.0 mM Ni<sup>2+</sup> induces a characteristic "bundling" morphology of MT. Unlike taxol, a drug promoting MT assembly *in vitro* and *in vivo*, Ni<sup>2+</sup>-induced MT bundles were both Ca<sup>2+</sup>- and cold-sensitive.

### Publications

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## Occupational Stress and Health of Women LPN'S and LSW'S

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Program Area: *Psychological Disorders*  
Grant Number: *5 R01 OH01968-04*  
Start & End Dates: *12/01/84 - 03/31/89*  
Funding Level: *\$212,952 (\$806,221 Cum)*

### Importance to Occupational Safety and Health

This study provides important information about the relationship between occupational stress and health among women employed as licensed practical nurses or licensed social workers. It identifies the specific aspects of job experience that are negatively and positively related to health. The study also examines the contributions of multiple role occupancy and of the experiences in family roles among employed women.

### Objectives

The short-term longitudinal interview study of women who are licensed practical nurses ( $n = 156$ ) and licensed social workers ( $n = 258$ ) focuses on the relationship between work and non-workplace stressors and health-related outcomes in women. Building on the investigators' prior research, the study extends our understanding of occupationally-based psychosocial stress to include not only job conditions but also: (1) occupancy of non-workplace roles and (2) the quality of experience in occupational and non-workplace roles.

Two categories of outcomes are examined: (1) physical health indices, including both self-reports and blood pressure measurements and (2) mental health indices, including anxiety, depression, and psychological well-being.

Major hypotheses concern the effects on physical health, psychological distress, and psychological well-being of job role quality, occupancy of non-workplace roles, and quality of roles. In addition, social support is examined as a possible moderator of the relationship between stressors and health outcomes.

### Methodology

A disproportionate, stratified sample (race, parental status, partnership status) of LPN's and SW's, ages 25 to 55, who live within specified zip codes (an approximately 25-mile radius of Boston) was drawn randomly from the professional registries of the two occupations. By enlisting the cooperation of relevant groups and publicizing the study widely, we have obtained an excellent response rate of 96.6%. In individual interviews, a variety of measures—both standard scales and scales developed for this study—assess role quality (the balance between rewarding and distressing attributes of a role), psychological distress, and physical health (including blood pressure). During the four years of the project, data were gathered at three points in time, one year apart. A 10% random sample of subjects was reinterviewed to establish the test/re-test reliability of certain scales.

### Significant Findings

The major findings are:

1. Among female health-care providers, work-role quality is an important predictor of mental and physical health measures, particularly, psychological distress, subjective well-being, physical-health symptoms, and cardiovascular disease.
2. To fully understand the relationships between work-role quality and health measures, one has to take into account both the rewards and the concerns experienced at work and their interactions. To illustrate, the work-reward factor helping others at work has direct effects on three health measures—subjective well-being, psychological distress and physical symptoms. Moreover, helping others at work moderated the effects of overload on all three health measures. However, helping others was not associated with the onset of CVD. These findings provide only partial support for the Karasek job-strain model.
3. With psychological distress as the outcome, women with family roles are less reactive, i.e., more resilient, to the presence or absence of particular work rewards and concerns. In contrast, with physical symptoms as the outcome, employed women with the children are more reactive to the presence or absence of rewards from satisfaction with salary than are women without children.
4. With psychological distress as the outcome, partner-role quality has direct effects only, and parent-role quality has both direct and

interactive effects. The significant interaction reflects positive-spillover effects from work to home: employed mothers with troubled mother-child relationships are protected from the distress-increasing effects of these relationships provided they are in rewarding jobs.

5. Over time, the sample was extremely stable with respect to role occupancy, role quality, and health measures.
6. Changes in work-role quality were related in the expected direction to changes in well-being and in psychological distress.
7. Parental status had a significant interactive effect on the relationship between changes in work-role quality and changes in psychological distress: change in psychological distress among employed women who are not mothers, compared to those who are mothers, is more vulnerable to change in work-role quality.
8. The interaction of change in work-role quality by change in parent-role quality is significantly related to change in psychological distress. If both work-role quality and parent-role quality improve, distress decreases. However, if work-role quality declines, even an increase in parent-role quality can not reduce psychological distress.

#### Publications

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Baruch GK, Biener L, Barnett RC: Women and Gender in Research on Work and Family Stress. *American Psychologist* 42:130-136, 1987

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### Job and Family Stress and Women's Work Performance

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Program Area: *Psychological Disorders*  
 Grant Number: *1 R01 OH02162-01A1*  
 Start & End Dates: *02/01/87 - 12/31/88*  
 Funding Level: *\$118,781 (\$141,486 Cum)*

#### Importance to Occupational Safety and Health

The results of this study of job stress and satisfaction have implications for worksite health promotion programs. Excessive job pressure is a detractor for both clerical and blue-collar workers, while feeling valued is the most important contributor to satisfaction. Younger workers seem especially vulnerable to stress and lower satisfaction; important stressors include child care concerns, job security, and episodes of discrimination. In addition, family factors affected overall job stress and satisfaction. These results suggest guidelines for prevention and intervention programs.

Family satisfaction and stress outcomes show the important interaction of work conditions on family well-being, as well as the reciprocal. Most studies to date have not looked at this bidirectionality. Further analyses will examine the outcomes of these factors on various worksite-related concerns, e.g., health, performance.

Our substance use findings are of special interest to work organizations, particularly employee assistance programs, as well as prevention and treatment efforts directed toward women.

#### Objectives

The purpose of this investigation is to increase knowledge of the roles family and work factors play in working women's job performance. We propose a process model which suggests that work and family environments are related to certain repertoires of behaviors in a manner reflecting individual differences; these outcome behaviors,

conceptualized as forms of functional or dysfunctional coping, include substance use, illness, accidents, and job performance.

### Methodology

Local unions and trade organizations cooperated in providing lists of traditionally-employed women who were school secretaries and clerical workers and non-traditionally-employed women who were city transit workers and skilled trade and craftspersons. Each woman was mailed a questionnaire with a cover letter explaining the study and offering ten dollars for her anonymous participation. Two reminder post cards were sent at three- and five-week intervals.

Questionnaires were mailed to 700 clerical workers, 391 city transit workers, and 120 blue-collar trade and skilled craft workers. A total of 611 questionnaires were returned for an overall return rate of 50.5%, with a 60% return rate (n=72) for the trade and craftspersons, a 56% return rate (n=391) for the clerical workers, and 39% return rate (n=148) for the transit workers.

### Significant Findings

The purpose of this study was to examine home and job stress in relation to working women's job performance. Job stress and satisfaction were investigated for traditional and non-traditional workers. For both occupational groups, satisfaction was greater for older workers; stress was greater for younger women in the domains of child care, security, and discrimination. Using hierarchical block design analysis, we identified the most powerful predictor of job satisfaction to be intrinsic job variables (feeling valued, less pressure on the job) for both clerical and blue-collar workers; family satisfaction also predicted satisfaction at work. Intrinsic job characteristics also were the most important predictors of job stress, again for both occupational groups; family stress also contributed to job stress.

Overall, mean family stress was found to be at a moderate to low level. No significant difference was found between clerical and blue-collar women's assessment of such stress. Also, there was no significant difference in the assessment of family stress between four family groups examined (married with children, unmarried with children, married without children, and unmarried without children).

Predictors of family stress were determined separately for the two employment categories of women and the four family groupings through the

use of hierarchical regression analysis. Current self-reported health status predicted the level of family stress for every group of women studied. Depression was the personality trait most frequently associated with family stress. Concern over a partner's or child's substance abuse was the factor from the home environment most frequently predictive of family stress, while job stress was also a significant predictor. These predictive models explained from 36 percent to 59 percent of the variance in family stress for the various groups of women.

Our data show that a majority of the women are not using illicit drugs or are using them very infrequently. Only a very small number report using drugs or alcohol prior to or at work. As expected, alcohol and tobacco are the most used substances, followed by depressants and marijuana. Women in non-traditional jobs were most likely to use drugs of any kind. Those not married with no children were higher users of alcohol and tobacco than those in other family patterns.

Over half of the respondents do not use drugs in response to family stress, but many of those who drink almost daily indicate that they sometimes or often drink to cope with family problems. In addition, a large proportion of those who drink heavily do so in response to work. Use of drugs is lower for work stress than for family stress.

Non-traditional workers report concern about co-workers' drug use, while a substantial percentage in both groups are concerned about their spouse/partner's substance use. Further analysis will examine additional factors associated with various substance use patterns among employed women. Health and work performance outcomes will also be determined.

## Stress in One Occupational Group: Teachers

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Start & End Dates: *06/01/88 - 05/31/91*  
Funding Level: *\$82,839 (\$157,031 Cum)*

### Importance to Occupational Safety and Health

The purpose of the study supported by NIOSH/CDC is to document the impact of adverse occupational conditions on the health and morale of teachers. Despite their importance to our future, the conditions in which teachers work, particularly in urban public schools, are unsatisfactory in a number of ways. Instruments designed for the present study with the help of teacher informants and pilot research with veteran teachers yield data indicating that veteran and newly-appointed teachers are sometimes exposed to the threat of violence, disrespect from their students, and unsupportive supervisors. Preliminary results of the study indicate that such occupational conditions are linked to a number of health outcomes including depressive and psychophysiologic symptoms as well as problems in morale as reflected in job dissatisfaction and decreased motivation to continue in the profession. It is important to emphasize that the occupational conditions examined in this study are preventable.

### Objectives

The principal objectives of the study follow:

1. To compare the pre- and post-employment mental health (e.g., depressive symptoms, self-esteem), psychophysiologic symptoms, and health behaviors (e.g., smoking) of recent college graduates who enter the teaching profession with that of similar graduates who do not enter the teaching profession.
2. To identify the types of episodic job-related events and ongoing working conditions that affect the health and morale (job satisfaction,

motivation to remain in teaching, and exits from the profession) of new teachers. Alternative measures of job stressfulness (e.g., school-level teacher-assault rates), derived from public records, will also be examined in relation to teacher health.

3. To identify the types of resources, including personal dispositions (e.g., locus of control), social support from colleagues and supervisors, and coping strategies, that may affect health outcomes in teachers. The question of whether the resources directly affect health outcomes or mitigate the effects of the job-related stressors will be investigated.

### Methodology

Graduating students from the classes of 1988, 1989, and 1990 are recruited from among senior-year education and psychology courses and followed into their first jobs. The colleges from which the seniors graduate staff a great many positions in the New York City public school system. Individuals recruited from senior-year education classes are very likely to become teachers, and individuals recruited from senior-year psychology courses are very unlikely. Participants are followed longitudinally by questionnaire for up to three years, with measures obtained on them in the summer before entry into the workforce (Time 0, pre-employment), and then on two more occasions during the academic calendar (Times 1 and 2, generally post-employment). In the second and third years, data are also collected at three points in time.

The questionnaires comprise validated scales that supply information on health behaviors (smoking, coffee drinking, alcohol consumption, and obesity) and symptoms (psychophysiologic and depressive), non-occupational stressors, and social and psychological resources (e.g., social support from colleagues and noncolleagues, locus of control). Quitting and other types of job leaves are also ascertained. The study is prospective and includes pre-employment measures of the principal outcomes. A future feature of study, if expected support from the City University of New York becomes available, is a longitudinal pilot study to examine the link between working conditions and blood pressure with controls for pre-employment blood pressure.

### Significant Findings

The findings presented here are limited to women. On the average, women who became teachers had lower symptom levels than control

subjects in the summer just before entry into the workforce. Further analyses revealed no differences between teachers and non-teachers in symptom levels during the first fall in which the index subjects worked as teachers.

These are important findings because they suggest that, at least among newly appointed teachers, there are no untoward symptom effects in the group as a whole. Nonetheless, the teacher group showed considerable variability in symptoms, with some newly appointed teachers showing low levels, and other newly appointed teachers showing very high levels.

A series of multiple linear regression (MLR) equations were written to examine the effects of school conditions on health (depressive symptoms, psychophysiologic symptoms, and overall health) or health behavior (alcohol consumption, smoking, tranquilizer use) controlling for pre-employment levels and other factors (e.g., social class of origin, undesirable fateful life events).

The MLR equations indicated that the frequency with which the teachers encountered episodic stressors (e.g., threat of personal injury, confrontation initiated by an insolent student, episode of vandalism) and ongoing strains (e.g., overcrowded classroom, unmotivated students attending class, noise level in school, tendency of personnel to enforce rules against rule-breakers) was strongly related to increased levels of depressive and psychophysiologic symptoms and decreased levels of job satisfaction and motivation to continue in the profession.

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## Fundamental Investigation of Exhaust Hoods

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 Grant Number: *2 R01 OH02132-04*  
 Start & End Dates: *05/01/88 - 12/31/89*  
 Funding Level: *\$68,689 (\$339,963 Cum)*

### Importance to Occupational Safety and Health

This research is expected to produce a general optimization scheme to improve the efficiency of local exhaust hoods, which will reduce worker exposure as well as the cost of operating the exhaust system.

### Objectives

The long-term objective of this project is the optimization of exhaust hoods used in industrial ventilation, maximizing the capture ability and minimizing the air flow through the hood.

### Methodology

In order to carry out an optimization process, it is necessary to obtain tractable mathematical expressions of air flow generated by exhaust hoods under a wide range of circumstances which describe the operating parameters of the exhaust hoods as they may be used in an industrial operation. This portion of the study was carried out by obtaining the needed expressions utilizing potential flow theory and representative sink matching. The equations obtained were verified experimentally by the standard techniques of hot wire anemometry. The capture efficiency of hoods are being investigated using neutrally generated acetone vapor as the contaminant with air turbulence super-imposed upon the velocity field by means of a wake generated by a grid.

### Significant Findings

In the research carried out to date, we were able to construct mathematical expressions to predict air flow induced by free-standing flanged

exhaust hoods and experimentally verify these equations. The extension of these mathematical expressions to conditions where planes are adjacent to the hood at an arbitrary angle, and the experimental verification of these expressions, enabled us to extend the theoretical work to design conditions encountered often in the industry. The second, probably more significant accomplishment, was to develop a relatively simple optimization scheme for free standing exhaust hoods.

Relative to the original aims of the project, the accomplishments to date gave an optimization process which can be applied widely. The current research should provide the required design safety factor to extend the optimization procedures to a very wide variety of industrial situations.

### Publications

Esmen NA, Weyel DA: Air Flow Generated by Flanged Suction Hoods with Adjacent Planes. *Ventilation '88*. (ed. JH Vincent), Pergamon Press, London, in press, 1988

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## **Design a Systematic Engineering Control for Robotic System Safety**

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Start & End Dates: *01/01/88 - 12/31/89*  
Funding Level: *\$18,859 (\$53,490 Cum)*

### **Importance to Occupational Safety and Health**

As more and more robots are used in the workplace, the proper design of the robotic system becomes more important to prevent injuries. A review from this study showed that most robot-related accidents are preventable if the robotic system is properly designed and controlled. The study results provide a review of robot-related accidents, a review of guarding techniques for robots, a set of detailed guidelines for the planning, installation, and operation stages of robot use, and the principles and implementation of the design and control of a robotic cell. The study results can be applied to existing robots as an evaluation tool and to future robotic systems as a design guideline, thereby making the developed control system particularly useful for minimizing potential accidents that might be caused by robot use.

### **Objectives**

The objectives of this study were to develop a systematic procedure and guidelines for designing a robotic system, to construct a physical robotic system safety model according to the developed procedure, and to develop an intelligent software control system for monitoring the safety of the robotic system.

### **Methodology**

The study consisted of three phases. In Phase I, a systematic procedure and guidelines were developed for designing a robotic safety system. In Phase II, a physical robotic safety model cell was constructed. In Phase III, an intelligent software control system was developed for monitoring the robotic system.

### **Significant Findings**

It has been concluded from the results of this research that a robot cannot be considered as an individual unit in a manufacturing system, nor can any component (human operator, robot, robot controller, environment, or operational process) in a robotic system be separated and still effectively prevent robot-related accidents.

Specially, the following information resulting from this research is useful to the robotic system designer and user:

1. A review of the previous robot-related accidents data: From the analysis of the recorded 32 robot-related accidents, most of the accidents would have been prevented if appropriate safety design considerations were in effect.
2. Systemic engineering control guidelines for designing a robotic cell is developed: These guidelines are presented in the same format as a procedure analysis. The guidelines include planning, installation, and operation stages of robot use. The dangers, causes, effects and corrective measures are provided for each task in a certain stage of robot use. These easy-to-follow guidelines can be adjusted for a specific robotic application.
3. A review of the available machine guarding techniques for robot guarding: The review results show that most of the guarding techniques are still applicable to industrial robots with modifications to accommodate differences. This review is important not only from the standpoint of robotic applications but also as a response to an unanswered question: "Should robots be treated as traditional machines?"
4. Design for robotic cell safety: A robot usually works with other machines in a manufacturing system. When considering safety, attention should be given not only to the individual machines and robots, but also to their interactions to meet processing needs. The six severity level design (SSLD) concept was presented for safely designing a manufacturing cell. This design philosophy integrates guarding techniques with control actions, considers both production needs and safety concerns, and interfaces machine functions with process requirements. This philosophy has been implemented in an unmanned manufacturing cell that makes a family of parts. The hardware and software, as well as their interactions with the manufacturing process and control actions, are described. The design system has the advantage of providing maximum protection to

the operators while causing minimum interruption in production.

### Publications

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## Ventilation for Work in Confined Spaces

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 Start & End Dates: *01/01/87 - 12/31/89*  
 Funding Level: *\$98,997 (\$285,336 Cum)*

### Importance to Occupational Safety and Health

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

Ventilation is recognized as a primary means of engineering control—a means by which hazardous

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

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

### Objectives

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

1. Observe and evaluate ventilation characteristics of CS laboratory models, and describe guidelines for effective ventilation design.
2. Establish an empirical (regression) database representing the experimental characteristics and 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, chlorodifluoromethane, 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 multi-cell 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 multi-cell contaminant dispersion computer model was able to predict ventilation

effectiveness reasonably well for situations involving purging, continuous, and variable rates of contaminant release.

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### Artificial Intelligence in Process Plant Safety

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Start & End Dates: *06/01/88 - 05/31/90*  
Funding Level: *\$59,219 (\$141,129 Cum)*

#### Importance to Occupational Safety and Health

As modern chemical plants are extremely complex, they are more vulnerable to equipment failures, as witnessed by the recent chemical plant related accidents. Because of this complexity, modern plants are also more difficult to diagnose, thus raising serious occupational safety related problems. We are also dealing more with toxic substances, and with the advent of biotechnology and genetic engineering industries, the results of an industrial accident can be quite devastating. Occupational safety and health hazards pose a serious threat to an estimated 80 million workers in the United States. Industrial statistics show that even though major catastrophies and disasters of chemical plants are infrequent, minor accidents are

very common, occurring on a day-to-day basis, resulting in many occupational injuries and illnesses, and costing society billions of dollars every year. During 1983 the Bureau of Labor Statistics reported over 3,000 job-related deaths and an estimated 4.9 million job-related injuries and illnesses. It has also estimated that the annual cost to society of work-related injuries, illnesses, and deaths has nearly tripled from \$11.5 billion in 1972 to \$33.0 billion in 1984.

### Objectives

The major goal of this proposal is to research and demonstrate new approaches based on artificial intelligence (AI) towards the design of chemical process hazard detection, prevention, and control systems. Such systems are extremely important for improving the occupational safety of chemical plants owing to the complexity of modern process plants. Industrial statistics show that even though major catastrophes and disasters from chemical plant failures are infrequent, minor accidents are very common, occurring on a day-to-day basis, resulting in many occupational injuries and illnesses, costing the society billions of dollars every year. The proposed project is aimed at the prevention and control of such events through the development of model-based diagnostic reasoning methodologies using artificial intelligence techniques.

### Methodology

Past approaches in fault diagnostic systems did not properly include the human expert's reasoning strategies and experience and, hence, were not adequate in efficient and correct trouble-shooting. This is largely due to the fact that the past attempts did not incorporate AI techniques, an essential ingredient. In this project we propose a methodology that addresses the important research issues which are central to the development of knowledge-based systems for process fault diagnosis and hazard control with the following essential properties: process generality, fault diversity, reasoning transparency, and reliability and graceful degradation.

Knowledge-based systems utilizing the proposed methodology will diagnose using a combination of first-principles knowledge and compiled experiential knowledge rather than the compiled knowledge alone, as many expert systems now do. The methodology centers around the idea of utilizing a library of causal and fault models of the process units during the diagnostic reasoning process. As these models would be generic and process-independent, they would be applicable to a

wide variety of process configurations. This deep-level knowledge of the process would be integrated with compiled process specific heuristics in an object-oriented two-tier architecture. The proposed approach would also deal with the diagnosis of sensor failures and the analysis of process dynamics and transients. In this project, we will also investigate the automatic learning of diagnostic heuristics using a failure-driven learning technique.

### Significant Findings

We have successful preliminary results of this novel approach in the form of a prototypical expert system, called MODEX (Model Oriented Diagnostic EXpert), that has been developed for model chemical plants. MODEX reasons from the deep-level knowledge of the process, using information such as process constraints, confluences, causal and fault models of process equipments, and the overall structure of the chemical plant. An object-oriented architecture has been developed for facilitating knowledge representation and reasoning. We have also developed a framework for the integration of deep-level and compiled knowledge for process diagnosis. We have also demonstrated the automatic acquisition of diagnostic knowledge through a mechanism called causality-based failure-driven learning. A systematic analysis of the development of causal models of chemical processes has been achieved.

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## The Impact of Separation on Exposure and Hood Capture

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Start & End Dates: *09/29/87 - 09/28/89*  
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### Importance to Occupational Safety and Health

The research is expected to provide a fundamental understanding of the fluid mechanics governing the transport of gaseous pollutants generated from sources close to the body. The knowledge will be useful in improving control of worker exposure to airborne pollutants through the use of ventilation.

### Objectives

The primary objectives are: (1) the development of a mathematical model to estimate worker breathing-zone concentration when exposed to contaminants generated in the near-wake resulting from boundary layer separation; (2) examination of the factors, especially worker orientation with respect to the freestream direction, which influence exposure; and (3) extension of the model to local exhaust hoods and the examination of the relationship between exposure and hood capture efficiency.

### Methodology

Wind tunnel and local exhaust hood studies using anthropometric mannequins and sulfur hexafluoride as a tracer have been employed to examine mathematical models developed from (1) dimensional analysis and (2) numerical solutions of the Navier-Stokes equations. Infrared spectrophotometry is used to measure tracer gas levels in the mannequin's breathing zone.

## Significant Findings

Models relating breathing zone concentration to the Reynolds number (based on mannequin body dimension), source flow rate, and source-to-mouth distance have been developed and are in good agreement with experiments. Vortex shedding appears to be the predominant mechanism of contaminant transport when air flows behind the worker and the source is in the near-wake. Strouhal number is an important dimensionless parameter to characterize the transport process. Capture efficiency was inversely correlated with breathing zone concentration  $r = -0.79$ . The relationship between breathing-zone concentration and predicted capture velocity was weaker  $r = -0.20$ .

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## Fundamental Factors that Affect Dust Generation

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Start & End Dates: *12/01/88 - 11/30/90*  
Funding Level: *\$77,670 (\$77,670 Cum)*

### Importance to Occupational Safety and Health

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

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

## Objectives

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

1. Develop a test that measures dustiness. We will develop 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 will investigate 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 will evaluate 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 reduced 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 non-respirable particles, larger than  $25 \mu\text{m}$  in aerodynamic diameter. At the outlet of this column is a high-volume cascade impactor, which sorts the respirable particles by aerodynamic size. Air entrained with the column of falling material is measured independently with a bleed system. Experiments reported here measured the reproducibility of this test procedure as well as the generation rate and size distribution of an aerosol produced by dropping sand 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 affected 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.

Variables that affected generation rate did not necessarily affect size distribution, and vice versa. Results from this work are correlated mathematically. We have developed a method to determine the generation rate and size distribution.

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## Worker Perception of Hazardous Robotic Workstations

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Program Area: *Control Techniques*  
 Grant Number: *1 R01 OH02568-01*  
 Start & End Dates: *06/01/88 - 05/31/89*  
 Funding Level: *\$26,539 (\$26,539 Cum)*

## Importance to Occupational Safety and Health

Today's industrial robots perform their tasks with high speed movements, unpredictable motion patterns, and variable working envelopes or danger zones. Robot operators have been seriously injured and killed due partly to misapprehension of these nontraditional characteristics of industrial robots. This research addresses the perceptual hazards associated with robotic systems and offers experimental data to design and maintain safer robotic workstations. The results of this study are expected to be used in NIOSH recommendations and ANSI standards for safe design and operation of robotic workstations.

## Objectives

The long-term goal of this extensive research area is to investigate the perception, decision, and action processes involved in collision and injury avoidance with respect to both expected (but unnatural) and unexpected robot movements. In particular, the objective is to study workers' perceptions of the operational characteristics of two industrial robots, and relate these perceptions to potential hazards created by the human-robot interactions.

## Methodology

Twenty-four industrial workers from the metropolitan Louisville area, who had previous exposure to automated systems and robotics, participated in the study. Two industrial robots, i.e., P50 and MH33, were used in three laboratory experiments.

Experiment #1 investigated workers' perception of robot speed and determined the maximum speed that human operators judged to be "safe" for working close proximity to robot installations and monitoring robot actions. As an industrial robot performed a simulated 15-minute pick-and-place palletizing task, the subjects were instructed to adjust the robot's arm speed (faster or slower) until a maximum but "safe" speed was determined. To protect the subjects, all the experimental sessions were conducted with subjects positioned outside the robot's working envelope using empty robot grippers. A two-factorial (2 x 2) design, with two levels of robot size (small = P50, large = MH33) and one replication for robot speed (25 and 90 cm/s), and two levels of exposure to a simulated accident (yes, no) involving a robot hitting the mannequin placed inside the robot's working envelope, was used.

Experiment #2 investigated the minimum amount of time for robot inactivity (idle time) perceived by the workers as either a programmed stop or system problem such as malfunction, and an indicator of the safe-to-approach condition. Random stops of different durations were introduced into a 15-minute palletizing task. The subjects were instructed to indicate which stops they perceived to be preprogrammed and which ones were due to possible malfunction needing the operator's intervention. Subjects were asked to determine how long to wait before they felt it was safe to enter the robot's work envelope in order to correct the simulated system problem. A two-factorial design (2 x 2) with two levels for robot size, replication for robot speed, and two levels for exposure to a simulated accident, was used.

Experiment #3 investigated workers' perception of the robot working envelope. After demonstration of a 15-minute palletizing task, the main power source of the robot was shut down, and the subjects were instructed to approach the robot's work area from six different direction angles. The subjects were divided into two groups of twelve workers each. One group was instructed to determine the maximum reach of the robot's arm (reach zone), while the other one was to determine the limits of a safe zone around the working robot (safe zone). A mixed, three-factorial design (2 x 2 x 2) with the instruction type (reach zone, safe zone), robot size

(small, big) and accident exposure (yes, no), and two nested factors (2 levels of robot speed and 6 levels of approach), was used.

## Significant Findings

Experiment #1. The analysis of variance showed that the effects of robot size and initial speed of robot's arm on the selection of maximum speed of robot motions perceived as safe for monitoring purposes were significant at  $p < 0.01$ . The exposure to a simulated accident, however, did not affect the selected speed values. In both cases, the average selected speed was 57.5 cm/s ( $p > 0.05$ ). On the average, workers selected the speeds of 63.8 cm/s and 51.3 cm/s for small (P50) and large (MH33) robots, respectively. When the speed adjustment process began at 90 cm/s, workers selected significantly higher levels of maximum safe speeds ( $x = 62.3$  cm/s) than they did when the initial speed of the robot's arm was only 25 cm/s ( $x = 52.7$  cm/s).

Experiment #2. Robot size and accident exposure to a simulated accident significantly affected the length of waiting times chosen by the workers for the safe-to-approach condition. The robot's initial speed (25 or 90 cm/s) and replication did not influence the perception of idle times ( $p > 0.05$ ). The effect of interactions was also not significant. On the average, workers waited longer ( $x = 22.7$  s) before entering the small robot's work envelope than they did for the large robot ( $x = 16.3$  s). Workers who witnessed the simulated accident also waited longer before they decided it was safe to approach the robot ( $x = 22.4$  s) than those who did not see the accident ( $x = 16.6$  s). Five percent of the worker population selected the times of 8.3 s and 6.4 s or less (5th percentile value), for small and large robots, respectively, while 95% of the workers waited 37.0 s and 26.4 s or less (95th percentile value), respectively, before entering the P50 or MH33 robot's work envelope.

Experiment #3. The effect of instruction type (perception of the maximum reach of robot's arm versus safe zone around the robot) was highly significant ( $p < 0.00001$ ). Workers selected much smaller distances from the robot's work envelope ( $x = 3.4$  cm) when instructed to determine the maximum reach of the robot's arm than when asked to determine the safe zone around the robot ( $x = 28.3$  cm). In both cases, exposure to a simulated accident, robot size, robot speed, and the angle of approach towards the robot's work envelope significantly affected ( $p < 0.0001$ ) the distances chosen by the workers. In general, those who were exposed to the simulated accident kept farther away from both robots ( $x = 24.4$  cm) than

those who did not witness the accident ( $x = 7.3$  cm). Compared to the selected distances at the robot's speed of 25 cm/s ( $x = 12.9$  cm), the high speed of robot motions (90 cm/s) kept workers at a greater distance from the robot ( $x = 18.8$  cm). On the average, workers came closer to the work envelope of the large robot ( $x = 9.5$  cm) than they did in the case of the smaller robot ( $x = 22.2$  cm). Finally, workers chose significantly smaller distances in front of the robot than on the robot's left side or right side.

The analysis for the number of intrusions into the robot's work envelope showed that 90.2% of all intrusion cases occurred when workers attempted to perceive the maximum reach of the robot's arm. Intrusion made by the workers who were exposed to the simulated accident accounted only for 25.9% of all intrusions. The number of intrusions was significantly higher when working with the bigger robot (69.2%) than when working with the smaller one (30.8%), and when the speed of robot motion was 25 cm/s (60.8%) versus 90 cm/s (39.2%). Finally, there were significantly more intrusions into the robot's work envelope when approaching the robot in two front paths (52.4%) than on its left (23.7%) and right (23.7%) sides.

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## Field Study of Local Exhaust Ventilation Performance

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 Start & End Dates: *09/28/89 - 09/27/92*  
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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 the strong possibility of lower operating costs if the solvent is recovered from the local exhaust system.

#### Objectives

The broad long-term objective of this research is to answer the question: Can exterior hood design be improved to adequately control emissions from open surface tanks?

The specific aims of the research are to answer the following questions: (1) Can laboratory validated capture efficiency models be used to predict capture efficiency of local exhaust hoods in industrial settings? (2) Can industrial crossdrafts

be quantified and characterized? (3) Can activity parameters be correlated with measured crossdrafts and capture efficiencies?

### Methodology

The project involves conducting 18 field studies, six in the first year and twelve in the second year, at a rate of one per month. Three sets of measurements will be done during each study to answer the questions asked in the specific aims.

During idling conditions, tracer gas will be released through a series of tubes, with holes drilled in them, configured to fit over the surface of the vapor degreaser. Sulfur hexafluoride (SF<sub>6</sub>) will be released at a measured rate, and concentration of SF<sub>6</sub> will be measured in the duct downstream of the hood. The air flow will be measured, along with the hood and tank dimensions. These measurements will allow for calculation of capture efficiency. Simultaneously with the SF<sub>6</sub> measurements and during operational periods, solvent concentration will be measured in the duct and at several distances from the degreaser. This will allow for calculation of emission rates from Fick's Law and the concentration gradient. The duct concentration and emission rate will also allow for calculation of capture efficiency.

The simultaneous measurements will give independent validation of the emission factor approach as a method of measuring local exhaust hood capture efficiency. The SF<sub>6</sub> measurements will be limited to idling conditions because the SF<sub>6</sub> release apparatus will interfere with operation of the degreaser. The emission factor approach will be used to measure hood capture efficiency during production times.

Crossdraft velocity (magnitude and direction) will be measured simultaneously with measurement of capture efficiency using a two-dimensional hot-wire anemometer.

Capture efficiencies measured each hour will be compared with model predictions. The magnitude of the crossdrafts will be tabulated for use in the design of future experimental work. The turbulence characteristics of the crossdrafts will be measured. These characteristics will be analyzed to determine how close (or different) they are from those used in the laboratory development of the capture efficiency model. The model may need to be adjusted for any significant differences.

Activities involving the degreaser (loading and unloading of parts, opening and closing of cover, size and shape of parts, etc.) and activities in the vicinity of the degreaser (workers walking, standing, or sitting near the degreaser, use and location of cooling fans, location of general ventilation supply

and exhaust openings, etc.) will be recorded during each hour that sampling is conducted. Recorded activities will be correlated with recorded crossdrafts to determine how specific activities are related to measured crossdraft characteristics.

### Significant Findings

This research project was begun on September 28, 1989. We are in the process of ordering equipment and arranging access to industrial sites. The first site visit is scheduled for January 1990. To this point, there are no significant findings which have resulted from this project.

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## Tractor Stability Information Processing System

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Program Area: *Control Techniques*  
Grant Number: *5 R03 OH02236-02*  
Start & End Dates: *09/29/87 - 09/28/89*  
Funding Level: *\$16,743 (\$37,521 Cum)*

### Importance to Occupational Safety and Health

Agriculture as an occupation has the highest fatality rate per 100,000 workers of any major industry. Tractor overturns are responsible for approximately 40% of all agricultural work deaths. In addition to fatalities, tractor overturns cause loss of limbs, equipment damage, and equipment down time. The proposed instrumentation could also be utilized in the forestry, construction, and transportation industries to increase safe operation of off-road, self-propelled machinery.

### Objectives

The long-term objective of this research is to reduce fatal farm tractor overturn accidents. This project represented the second step toward the long-term goal and had three parts. One was to build a fully enhanced model tractor to verify and refine equations that continually provide tractor operators with stability and instability information. The second part was to explore human/machine interfacing for development of appropriate feedback

instrumentation. The third part was field testing with full-size tractors to learn more about the roll roughness coefficient.

### Methodology

A one-eighth scale model tractor equipped with rear wheel differential, a scaled power plant, pneumatic front and rear tires, and a fully operational steering system was constructed. A data acquisition system was designed. This tractor was used to refine and validate previously derived stability equations. A human factors literature search of related fields was conducted and a theoretical model was developed. The model was used to develop a tractor simulator and experiments. Field tests with full-size tractors did not materialize.

### Significant Findings

1. Testing on a sloped terrain board indicated that a previously derived stability equation predicts conservative critical velocity values. That is, the observed speed at which the model tractor rolled over, given a set of parameters, was greater than what the mathematical model predicted it should be. The degree of the conservative prediction varies with the slope of the terrain board.
2. A data acquisition system was designed to collect accelerometer readings from the scale model tractor. It will be possible to use this same instrumentation system on full-size tractors in field tests.
3. The enhanced scale model tractor has proven to be a limiting factor in the validation of the stability equation. It appears that the tire/surface interaction cannot be sufficiently accounted for by the scale model tractor. Further study of the scale model tractor is needed before it can be used to accurately validate the mathematical model.
4. There has been very little study of tractor operators perception of imminent overturn, or of methods to provide a closed loop information feedback system. The need for such a system require the study of overturn perception, movement time for hand and/or foot responses, and mechanical delay of the tractor.
5. A three-axis farm tractor simulator was constructed to support theoretical modeling and empirical testing of operator perception, decision-making, and responding to imminent overturn. The simulator can effectively

simulate pitch, roll, and yaw motions that are commonly encountered in the field.

6. Six experiments have been designed to better understand perception and response to tractor instability.

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## Reducing Solvent Exposure of Auto Body Workers

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Grant Number: *1 R03 OH02422-01*  
Start & End Dates: *09/29/87 - 09/30/89*  
Funding Level: *\$21,887 (\$21,887 Cum)*

### Importance to Occupational Safety and Health

Auto body repair shops use large quantities of organic solvents in settings which commonly have inadequate engineered protective systems. Employees are therefore at risk for potential solvent-related health problems, such as neurologic disease. Personal protective equipment probably provides the best means of individual protection in this environment, but in general such equipment is underutilized by most workers in this industry. Since the use of personal protective equipment is

highly dependent upon the individual worker's degree of motivation, an educational program which incorporates exposure information derived from the individual worker's personal situation might provide a better basis to motivate use of personal protective equipment.

Unlike air sampling, the measurement of many solvents in exhaled breath or body fluids can assess an individual's exposure to those solvents by skin as well as inhalation routes. Breath sampling is relatively non-invasive and is sometimes more acceptable to individuals than is collection of blood or urine. However, exhaled breath measurements can be logistically difficult to perform, and most of the available techniques do not allow rapid quantification of solvent levels in breath. A breath sampling device which provides individual exposure information in a relatively rapid and reliable manner and which can actually be readily deployed in the worksite could be a valuable component of an educational program which emphasizes individual rather than generic information.

### Objectives

The objectives of the study were to demonstrate that:

1. The use of personal protective equipment can effectively reduce personal exposures to organic solvents in the auto body repair industry.
2. An exhaled breath sampling device, which uses a dual sorbent cartridge collection system on a modified half face air purifying respirator and which can be worn by a worker while performing nonexposure work activities, can be used in the field to assess an individual's solvent exposures and to provide reliable exposure information within 24 hours of measurement.
3. The results of personal breath sampling for exhaled solvents can be an effective component of an educational program to motivate individual workers to use skin and respiratory personal protective equipment.

### Methodology

The study involved eleven painters and assistant painters in five auto body repair shops. The level of exhaled toluene was sampled in each participating worker's breath prior to work shifts on Monday, Tuesday, Wednesday, and Thursday of the week and prior to the institution of a new educational program encouraging use of personal protective equipment. Airborne toluene was monitored throughout each work shift using personal charcoal

passive dosimeters and also during the breath sampling session using charcoal tubes and a personal sampling pump. During the subsequent week, participants were given their individual breath and air sampling results as part of an educational program which focused on the health effects of paints and solvents and on the proper use of gloves and respirators. Appropriate gloves and respirators were provided, along with replacement supplies. Qualitative respirator fit testing was performed. Breath and air sampling were repeated using identical protocols after 2 weeks and again after 6 weeks.

### Significant Findings

1. No measurable effect of the motivational intervention program was observed in these auto body painters. One painter demonstrated reduced exposure levels after the intervention; however, the variability of the data precluded a definitive conclusion about any contributory effect of the intervention. Any solvent exposure reduction which may have been present in this subject sample was overshadowed by the uncertainty in exhaled breath measurements due to presumed leakage.
2. Respirator leakage was identified as a major confounding factor in exhaled breath sampling utilizing the dual sorbent half face respirator collection system.
3. Respirator leakage is non-uniform and displays high intersubject and intrasubject variability. This non-uniform response combined with insufficient information about the leakage effect over a wide range of exposure conditions precluded the possibility of any adjustment of the expired breath measurements.
4. The dual sorbent collection system still may be a valid means for sampling of organic solvents in exhaled breath if tests are conducted in a noncontaminated atmosphere. The sampling system offers the advantages that it is a relatively simple, non-invasive, and readily acceptable by workers.

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## Glove Permeation by Semiconductor Processing Mixtures

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Program Area: *Control Techniques*  
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Start & End Dates: *07/01/89 - 06/30/90*  
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### Importance to Occupational Safety and Health

The permeation of solvents through gloves and subsequent dermal absorption may represent an important, yet unrecognized, route of exposure to hazardous chemicals used in semiconductor microfabrication facilities. Of particular concern are organic solvent mixtures containing glycol-ether (cellosolve) derivatives, several of which are recognized reproductive hazards that are readily absorbed through the skin. Other solvents used in these processes have the potential to cause local skin irritation as well as adverse systemic effects. In addition, new formulations are being introduced that contain solvents for which little or no toxicological or glove permeation data are available.

It is well known that the permeation behavior of a mixture of chemicals through protective gloves often cannot be predicted from the behavior of the pure components of the mixture. Since published guidelines contain only limited data on the permeation of solvent mixtures and no generally applicable theoretical models for predicting mixed-solvent permeation have been developed, selecting the proper glove for protection against mixtures requires empirical testing. Increased temperature and repeated solvent exposure can also reduce permeation resistance for a given solvent/glove combination.

The information obtained in this study will aid in the assessment and control of dermal exposures to hazardous chemicals in the semiconductor industry. In addition, insight will be gained into the general problem of predicting mixed-solvent permeation through glove materials.

### Objectives

The specific objective of this study is to characterize the permeation behavior of several glove materials when challenged with organic solvent mixtures used in semiconductor manufacturing processes. An emphasis is being placed on determining whether, and to what extent, permeation is accelerated for mixed solvents relative to pure solvents. The effects of temperature and repeated exposure are also being investigated.

The broader objectives of this work are to provide information that will be useful in the evaluation of potential risks from dermal exposure to hazardous solvent mixtures and in the proper selection and use of gloves in semiconductor processing facilities. Correlations between permeation behavior and the chemical and physical properties of the solvent mixtures are also being sought in order to allow prediction of permeation behavior for untested mixtures.

### Methodology

The standard permeation test method, ASTM F739-85, is being used to determine breakthrough times and steady-state permeation rates at 25 and 37°C for five chemically protective glove materials commonly used in microfabrication facilities. Two surgical-type glove materials, often worn beneath the chemically protective gloves, are also being examined. Solvent mixtures being studied include resists and related lithographic formulations, as well as etching mixtures containing organic solvents. For glove materials exhibiting satisfactory permeation resistance upon initial exposure, additional tests are performed to determine whether repeated exposure reduces their permeation resistance.

### Significant Findings

Initial results have been obtained for a common photoresist thinner containing a mixture of cellosolve acetate, xylene, and n-butyl acetate and for a negative photoresist containing a mixture of xylene and methyl cellosolve. For both mixtures, the permeation of the cellosolve derivatives were accelerated in the presence of the other mixture components. For the photoresist thinner, gloves made of nitrile rubber and butyl rubber exhibited significantly longer breakthrough times than those made of natural rubber, a blend of neoprene/natural rubber, or a blend of neoprene/natural rubber/nitrile. However, nitrile glove samples allowed to air-dry for up to five days after an initial exposure were found to contain residual solvent upon re-testing. Surgical-glove

underlayers had a minor effect on breakthrough times and permeation rates. Exposure at 37°C reduced the breakthrough times for all gloves by approximately 50% and increased the permeation rates by more than 30% relative to exposure at 25°C.

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## Capture Efficiency of Local Exhaust Hoods

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Program Area: *Control Techniques*  
Grant Number: *1 R03 OH02680-01*  
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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 disturbances will be investigated and tabulated. Existing capture efficiency models developed for uniform crossdrafts will be used as the starting point for new model development. This new model will include the effects of turbulence scale and intensity on the spread of contaminant around streamlines.

### Objectives

The broad long-term objectives of any research of capture efficiency of local exhaust hoods should be: (1) to develop usable, practical, and validated models to predict hood performance; (2) to relate hood capture efficiency to workers' breathing zone concentration; and (3) to develop methods of ventilation design to maintain workers' breathing zone concentration below a specified level (e.g., Permissible Exposure Level, PEL, or Threshold Limit Value, TLV).

The specific aims of this research proposal are: (1) to investigate the turbulence parameters (intensity and scale) of typical crossdrafts or disturbances to air flow; and (2) to incorporate turbulence parameters into existing capture efficiency models.

### Methodology

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

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

The velocity in each of the situations listed will be measured, in a grid pattern in the area in front of the hood, using a hot-film anemometer with high frequency response suitable for turbulence recording. Velocity as a function of time will be recorded on a personal computer with an analog to digital converter. Turbulence intensity is defined as the square root of the sum of the squares of velocity fluctuation divided by the mean velocity. Turbulence scale is determined by performing a fast Fourier transform on the velocity data to get a power spectrum. Examination of the power spectrum reveals the scale of turbulence. A series of tables or graphs will be generated, from the velocity and turbulence data, for the four situations studied.

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

and turbulence intensity and scale constant. The results will be used to develop a model for capture efficiency.

#### **Significant Findings**

This research was begun in July 1989. In the first three months of the project, equipment was ordered and the laboratory prepared. The experiments are just beginning. To this point, there are no significant findings which have resulted from this project.

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## New Methods for Quantitative Respirator Fit Testing

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Program Area: *Respirator Research*  
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Start & End Dates: *09/01/87 - 08/31/90*  
Funding Level: *\$159,322 (\$689,292 Cum)*

### Importance to Occupational Safety and Health

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

### Objectives

The overall aim of this research is to study the basic mechanisms of air and aerosol penetration through face seal leaks and the filtering material, and to develop from this knowledge quantitative fit tests that are easy and inexpensive to perform. Two types of respirators in common use are studied: (1) disposable respirators which consist mostly or entirely of contoured filtering material, and (2) half-mask and full facepiece 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 and full facepiece 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 in respirators in actual use and is compared with available methods used on surrogate respirators.

### Significant Findings

Through use of a condensation nuclei counting technique for fit testing respirators, the traditional aerosol generator and exposure tent or booth are no longer needed. This simplification and cost reduction has increased the use of quantitative fit testing. The dynamic pressure testing technique (still under development) is further reducing the cost and making fit testing available for use on the actual respirator worn in the field. The new size-fractionating aerosol generator and a low-loss sampling probe and train provide the basic tools for measuring the significant characteristics of disposable respirators. From these data, new techniques suitable for disposable respirators will be developed.

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## Respirator Performance Model for Particulates

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Program Area: *Respirator Research*  
 Grant Number: *5 R01 OH01595-05*  
 Start & End Dates: *04/01/88 - 08/31/91*  
 Funding Level: *\$88,130 (\$336,594 Cum)*

### Importance to Occupational Safety and Health

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

### Objectives

The overall objective of this grant is to extend our understanding of the effect of particle size on the performance of air-purifying respirators for protection against particulate exposures. This is accomplished through experimental measurement of filter, exhalation valve, and facial seal leak performance as a function of particle size and 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, and (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 $\mu$ m. 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 evaluation of unimpaired exhalation valves is complete. Leakage for such valves ranges from less than 0.001 to .05%, increasing with work rate. The effect of a foreign object on the valve seat has been evaluated. An 0.1 mm foreign object on the valve seat can increase valve leakage by 2 to 3 orders of magnitude to about 1%. A detailed analysis of the effect of respirator dead space on averaged inhaled concentration has been completed. 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 our computer model may overestimate by 45% inhaled dose for half masks and by 90% for full-face masks.

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### Measure of Work Performance Decrement Due to Respirators

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Grant Number: *5 R01 OH01632-02*  
Start & End Dates: *03/01/87 - 10/31/89*  
Funding Level: *\$123,194 (\$257,441 Cum)*

### Importance to Occupational Safety and Health

The ability to quantitatively identify a decrement in work performance due to respirators is important to estimate the economic impact of such an effect as well as to evaluate differences in respirator design. Although this study was not able to make major distinctions between different types of respirators, a method to effectively measure work decrement was identified. Follow-up studies are needed to validate the results and compare them to effects seen in actual workplaces.

### Objectives

The specific aim of this project is to develop a generalized test procedure or measurement technique which can be used to determine quantitatively the decrement in worker performance resulting from the wearing of various respirators. The hypotheses of the project, thus, are that there is a measurable decrement in work performance caused by the wearing of a respirator, and that the amount of decrement will vary with factors attributable to each respirator.

### Methodology

These hypotheses have been examined by observing subjects' performances at three different levels of simulated work tasks while wearing one of three different types of respirators or no respirator as a control. A homogenous panel of twelve young, healthy, non-smoking, adult male volunteers was selected. The three levels of work tasks, (1) cognitive, or decision making, (2) psychomotor, or manual dexterity skills, and (3) moderate physical work (bicycle ergometer), were selected to represent a wide range of tasks. The three types of respirators, (1) a disposable dust filter mask, (2) a half-mask with high efficiency filter cartridges, and (3) a full-facepiece air line respirator with pressure demand flow, were selected to represent the most widely used types of respirators in industry. The performance criteria to be used for evaluation are, respectively by task, (1) test score, (2) skill score, and (3) oxygen consumption, as measure of exertion.

### Significant Findings

The results from the physical work task indicated approximately a 10% increase in oxygen consumption with the half and full face masks. This supports previous physiological findings and suggests that respirators can be an additive factor that will contribute to work performance decrement. The

effects of respirators on cognitive task performance are important, but difficult to evaluate. Considering the bias of the different difficulty levels of the tests used in the experiment, the results indicate that the respirators did not significantly affect the performance of cognitive tasks. The psychomotor task test methods appear to be the best indicators of respiratory effects on work performance decrement. A steadiness task showed a 31% decrement for the full-face respirator. The One-Hole Test, which includes a number of sub-tests which can be evaluated, indicated an average movement time decrement of 16%. The other one-hole test indicators also showed decrements, but were lower and not statistically significant.

In summary, this research has:

1. Documented a statistically and potentially economically significant decrement in work performance due to the wearing of respirators.
2. Identified a psychomotor manual dexterity test instrument that can detect these decrements in work performance due to respirators, although it could not differentiate between respirators.

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## Respirator Tolerance

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 Grant Number: *5 R01 OH02005-06*  
 Start & End Dates: *09/16/87 - 09/15/90*  
 Funding Level: *\$76,720 (\$573,602 Cum)*

### Importance to Occupational Safety and Health

Use of respirators is an important component of worker protection, particularly when engineering controls are not possible (e.g., in many hazardous waste control situations). To be effective in preventing illness, respirators must not themselves impose major stresses and must be adequately tolerated to be used in work. It is therefore essential to understand the effects of respirators on the user and to develop practical means to assess respirator designs for certification purposes.

Development of methods to include human testing in device certification procedures should improve their use.

### Objectives

This project is assessing both the physiologic and subjective responses to respirator use. In addition, the interactions among subjective, physiologic, and psychophysiologic factors are being clarified. The ability to use a human panel to assess respirator safety and compare different types is being tested.

### Methodology

Respirator effects are being assessed using actual respirators (both air purifying and atmosphere supplying) and surrogates (which allow testing of individual load components). Studies are performed in several volunteer groups: healthy non-users, respirator users, and persons reporting more than average subjective discomfort. Measurements include ventilatory parameters, selected respiratory control parameters, subjective response, and psychophysiologic sensitivity to added loads. Studies are performed in controlled laboratory settings and under field conditions. The current studies include making multiple measurements over time in the same human panel members to assess stability of responses. In addition to exercise laboratory methods, the studies also employ respiratory inductive plethysmography techniques.

### Significant Findings

The effects of respirators are complex, affecting many different groups of variables. Physiologically, effects of flow resistive loading upon respiratory timing parameters are found. These effects are seen at all levels of exercise, are consistent among individuals, and they affect both normal and mildly impaired workers. Hence, both empirically and theoretically they appear to be likely to be useful for evaluating respirators as well as workers.

Subjective response can be measured quantitatively and with sufficient precision to be useful in comparing respirators. The subjective responses generally are well correlated with physiologic response, but there are certain situations in which subjectives add independent information. These findings suggest that such measurements should be seriously considered for inclusion in respirator certification procedures.

Psychophysiologic sensitivity to added loads is an individual characteristic which differs significantly

even among physiologically normal persons. It appears to be a significant determinant of subjective response as well as the magnitude of the physiologic effect. Furthermore, tolerance to respirator loads decreases such sensitivity. Therefore, it appears that there probably is an explanation for why there is variation in tolerance among workers.

Specific physiologic loads and respirator types have different effects. For example, inspiratory flow resistance appears to be more adverse than dead space loading. Powered air purifying respirators show disparity—they are of more benefit physiologically than subjectively.

### Publications

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Harber P, Barrett T, Shimozaki S, Kanter R: Respirator Effect in Pulmonary Impaired Subjects. *Am Rev Respir Dis* 139(4):A491, 1989

Harber P, Lew M, Shimozaki S, Thomas B: Non-Invasive Measurement of Respirator Effect at Rest and During Exercise. *Am Ind Hyg Assoc J* 50:428-33, 1989

Harber P, Shimozaki S, Barrett T, Loisesides P: Relationship of Subjective Tolerance of Respirator Loads to Physiologic Effects and Psychophysical Load Sensitivity. *J Occup Med* 31(8):681-86, 1989

Harber P, Soo Hoo K, Lew M: Effects of Industrial Respirators on Respiratory Timing and Load Sensitivity. *J Occup Med* 30:256-262, 1988

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## Asbestos Fiber Collection by NIOSH-Approved Respirators

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Program Area: *Respirator Research*  
 Grant Number: *5 R01 OH02154-02*  
 Start & End Dates: *01/01/86 - 12/31/88*  
 Funding Level: *\$49,254 (\$134,707 Cum)*

### Importance to Occupational Safety and Health

Asbestos is one of the leading causes of occupational lung disease. The recent emphasis on identification and removal of asbestos from homes, schools, and office complexes has created a new asbestos removal industry almost overnight. In many cases, workers who are poorly trained and inappropriately equipped are involved in this work. It is not uncommon for dust/mist respirators (not designed for use in asbestos laden environments) to be worn by asbestos removal workers. Little is known about the performance of these respirators when challenged with asbestos. This project assessed the efficiency of asbestos fiber collection of dust/mist respirators.

### Objectives

NIOSH procedures for certification of dust/mist respirators do not include tests to determine their performance in asbestos laden atmospheres. Instead, dust/mist filters are tested using silica aerosols. Further, standard NIOSH tests assess filter performance under conditions of steady flow. During actual use, the filters experience cyclic flow. Differences in the penetration of asbestos and silica could be significant—as could be the differences in filter performance under these two flow conditions.

The primary goal of this research was to assess the performance of dust/mist respirators when challenged with asbestos under cyclic flow conditions. A secondary goal was to evaluate the potential for predicting asbestos collection under cyclic flow using mathematical models or data from experiments using monodisperse latex sphere and/or silica aerosols.

### Methodology

The experiments were conducted in two phases. In the first phase, ten manufacturers' dust/mist filters were evaluated. Filter performance was assessed using eight sizes of monodisperse latex spheres—ranging from 0.1 to 2 micrometers ( $\mu\text{m}$ ) in diameter. These results were used to select respirators for further study.

In the second phase, three manufacturers' respirators were more carefully evaluated using asbestos and silica aerosols under conditions of steady and cyclic flow. Test conditions—i.e., aerosol size distribution, face velocity, humidity, etc.—in the steady flow silica experiments were similar to those used by NIOSH. The air flow pattern used in the cyclic flow experiments was designed to mimic human breathing during medium work. Silica penetration was determined by comparing the aerosol mass concentration upstream and downstream of the respirator filter. Test conditions in the asbestos experiments were similar except that UICC amosite was used in place of silica as the test aerosol. Asbestos fiber penetration was evaluated by comparing the numerical concentrations of fibers upstream and downstream of the respirator filter.

### Significant Findings

The overall mass penetration of the silica test aerosol—CMD 0.5  $\mu\text{m}$ , GSD of 2—was about 0.5% under steady flow. Mass penetration of silica was 50% greater under cyclic flow.

The typical count penetration of the asbestos—count median length 4.5  $\mu\text{m}$ , aspect ratio 9—was between 0.01% and 0.1% under steady

flow. For two manufacturers' respirators, asbestos penetration under cyclic flow was similar to that observed under steady flow. The third manufacturer's respirator exhibited valve failures under cyclic flow leading to substantially degraded performance.

#### Publications

Brosseau LM, Evans JS, Ellenbecker MJ, Feldstein ML: Collection Efficiency of Respirator Filters Challenged with Monodisperse Latex Spheres. *Journal of the American Industrial Hygiene Association*, in press, 1989

Brosseau LM, Ellenbecker MJ, Evans JS: Collection of Silica and Asbestos Aerosols by Respirators at Steady and Cyclic Flow. *Journal of the American Industrial Hygiene Association*, accepted, 1989

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### Theoretical Model: Pollutant Breakthrough on Sorbents

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Program Area: *Respirator Research*  
Grant Number: *1 R01 OH02260-01A2*  
Start & End Dates: *06/01/88 - 05/31/89*  
Funding Level: *\$97,397 (\$97,397 Cum)*

#### Importance to Occupational Safety and Health

The effects of humidity and contaminant concentration on respirator cartridge service life and on sampling devices are of considerable interest. The usefulness of these devices depends on the time required for a contaminant to break through the adsorbent under the specific conditions of use. It is not feasible to characterize (experimentally) the breakthrough properties of the devices under all conditions of potential use. Theoretical considerations have the potential, however, of predicting device performance for many different conditions. A theoretical model addressing contaminant breakthrough has been developed.

#### Objectives

Previously, a theoretical model was developed addressing respirator cartridge contaminant breakthrough; the model was applied to experimental data. The objectives of this study were:

1. To extend the application of the model to additional experimental data sets, and to derive theoretical parameters for ~100 additional contaminants.
2. To apply the theoretical model to investigate the effect of relative humidity and contaminant concentration on respirator cartridge breakthrough properties of selected contaminants.
3. To apply the theoretical model to study the contaminant breakthrough properties of charcoal tube sampling devices.

#### Methodology

Three important mathematical expressions were derived from the theory:

$$\text{Equation (1): } t = \tau + (1/k') \ln[P/(1-P)]$$

$$\text{Equation (2): } \log t = K'' - a \log C$$

$$\text{Equation (3): } W_t = CF[t - (1/k') \ln(1 + e^{-k'(t-\tau)})]$$

If  $\tau$ ,  $k'$ ,  $K''$ , and  $a$  are known for specified experimental conditions, Equations (1) and (2) may be applied to calculate the breakthrough time ( $t$ ) as a function of contaminant concentration ( $C$ ). The theoretical model was applied to experimental data to derive the required parameters; these parameters were employed to calculate the respirator cartridge breakthrough properties of ~100 different pollutants. The theory was also applied to assess the effect of humidity and contaminant concentration on respirator cartridge performance. Values of pertinent theoretical parameters were determined and used to calculate breakthrough curves under specified experimental conditions. In addition, the total weight of contaminant adsorbed on the charcoal was calculated [Equation (3)] for specified times of exposure.

#### Significant Findings

The values of required theoretical parameters were determined for ~100 compounds. Specific compounds were selected from the following types: aromatic compounds, alcohols, acetates, alkanes, and ketones.

The theoretical model was developed further to examine the effect of both test humidity and contaminant assault concentration on respirator cartridge service life. This study addressed a contaminant concentration range of 250-2000 ppm and test humidities ranging from 0% to 80%. The preconditioning humidity was fixed at 50%. The compounds studied were benzene and methyl chloroform. Theoretical parameters,  $k'$  and  $\tau$ , were described and values of these parameters were determined for various experimental conditions. Available experimental data were used for these determinations. The calculated values of  $k'$  and  $\tau$  were applied using derived theoretical expressions to generate each of several complete theoretical breakthrough curves for benzene and for methyl chloroform at specified contaminant assault concentrations and test humidities. The effect of humidity on the value of an additional theoretical parameter,  $a$ , was investigated. Values of this parameter and the parameters  $k'$ ,  $\tau$ , and  $K''$  were determined for specific test conditions. These values were substituted into pertinent theoretical expressions to produce a complete set of breakthrough curves.

The theoretical model was also applied to investigate contaminant breakthrough on charcoal sampling tubes. Associated with the model are two important theoretical parameters,  $k'$  and  $\tau$ . Values of  $k'$  and  $\tau$  were determined for n-heptane at five different concentrations. These values were used along with pertinent theoretical considerations to calculate the entire (0-100%) breakthrough curve for n-heptane collected with charcoal sampling tubes. In addition, available experimental data for perchloroethylene, isobutyl acetate, ethyl acetate, and dichloromethane were used in conjunction with the theory to generate theoretical breakthrough curves over the entire range of 0 to 100%. The theory was extended to calculate the weight of contaminant collected on the sorbent at 10% breakthrough.

#### Publications

Yoon YH, Nelson JH: Effects of Humidity and Contaminant Concentration on Respirator Cartridge Breakthrough. *Am Ind Hyg Assoc J*, in press

Yoon YH, Nelson JH: A Theoretical Study of the Effect of Humidity on Respirator Cartridge Service Life. *Am Ind Hyg Assoc J*, 49(7):325-332, 1988

## Respiratory and Thermal Physiology of Face Masks

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Program Area: *Respirator Research*

Grant Number: *5 R01 OH02564-02*

Start & End Dates: *05/01/88 - 04/30/91*

Funding Level: *\$254,263 (\$122,634 Cum)*

#### Importance to Occupational Safety and Health

When workers who are unavoidably exposed to dusts, fumes or noxious gases in the workplace wear appropriate respiratory protective devices correctly, they avoid the potentially harmful effects on the lungs of exposure to such substances. Though well designed, carefully manufactured, and thoroughly tested, such devices are implicitly uncomfortable to wear and produce some inconvenience or interference with the accomplishment of the task to be performed by the worker. Experience has shown that despite their need in appropriate circumstances, such devices may not be put on by the worker. Any improvement in the comfort of respiratory protective devices would be highly desirable because it would eliminate an obstacle that prevents workers from wearing them.

#### Objectives

The overall objective of this study is to pinpoint the factors that cause discomfort of respiratory protective devices, and eliminate them if possible. To remove the source of the discomfort, it is necessary to know its cause. Studies supported by this grant have shown that the air in face masks is hot and humid, that the skin temperature of the wearer's face increases, and that the unaccustomed warmth of the face is accompanied by discomfort which is reduced when the air around the face is cool and dry. The resulting hypothesis has been that the dominant factors contributing to discomfort of respiratory protective devices are the elevation of temperature of the skin of the face, and skin wetness due either to sweating or condensation of water vapor on the face.

Current objectives are to evaluate thermal discomfort in relation to other sources of discomfort and inconvenience of respiratory protective devices,

to decrease thermal discomfort to a minimum by modification of face masks to remove heat from the mask, and to diminish re-inspiration of heat and moisture accompanying either tidal breathing or delivery of a continuous air supply.

### Methodology

In studies described in the publications cited below, it was shown that the comfort and acceptability of air around the face depended on the temperature and humidity of the air, the temperature of the air surrounding the body of the subject, and the state of rest or exercise. A flow-through mask and continuous air supply were used to supply air to the environment of the face. Psychophysical rating scales were used to assess the comfort or discomfort of the subject. Thermocouples and a dewpoint sensor were used to measure the air temperature and humidity in the chamber supplying air to the face and in the air leaving the mask, as well as in the environmentally controlled room. A thermocouple was taped to the face, and multiple thermocouples to other cutaneous regions to monitor mean skin temperature. Recent experiments have used face masks with tidal breathing, accompanied by re-inspiration of dead space air, heat, and water vapor.

Psychophysical ratings and skin temperature of the face were measured. A dummy mask was constructed of aluminum and its walls cooled by evaporation of water from a cotton cloth adherent to its outer surface. The comfort and skin temperature obtained on subjects wearing this cool mask were compared with those of the same subjects wearing a nuisance dust mask (3-M 9913 Dust-Mist) and a rubber mask which had inspiratory valves with canister filters and an expiratory flap valve (Willson model 122510). Sensations of comfort, warmth, and skin wetness were plotted as a function of skin temperature on the face of the subject, and the regression lines were compared with those obtained previously using the flow-through air supply.

### Significant Findings

The most significant finding is that when skin temperature of the face is used as a basis for comparison, the ratings of warmth, wetness, and comfort of the three masks that required tidal airflow were identical to the ratings at corresponding values of skin temperature when using the flow-through air delivery system. Yet the weight, configuration, deadspace, observers, recording equipment, and subjects were different. This means that the dominant factor was the

influence of air in front of the face on skin temperature and wetness of the face. Accompanying this, and perhaps of comparable importance, was finding that the mask which was cooled by evaporation of water from its outer surface was rated "comfortable." Whereas this may not be the best way to cool a mask, it does lead to the conclusion that if a mask can be cooled, it can be made comfortable despite the presence of other factors that make it inconvenient to wear. This points the direction to follow in order to reach the objective of making masks more comfortable, and therefore more frequently worn.

### Publications

DuBois AB, Harb ZF, Fox SH: Thermal Discomfort of Respiratory Protective Devices. Am Ind Hyg Assoc J, in press, 1990

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## Quantitative Respirator Fit Test by Negative Pressure

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Grant Number: *5 K01 OH00068-03*  
Start & End Dates: *08/01/87 - 07/30/90*  
Funding Level: *\$32,344 (\$97,144 Cum)*

### Importance to Occupational Safety and Health

Development of a portable, cost-effective respirator fit test method will facilitate the testing of respirators for field use and will provide a measure of respirator fit that is more representative of actual fit during use on the job.

### Objectives

The principal objective is to investigate the capabilities of a new quantitative respirator fit test method that seems to be less complex, more

portable, and more cost-effective than current methodologies. The new method is based on exhausting air from a temporarily sealed mask, thereby generating a negative pressure that replicates the inspiratory driving force for leakage into the mask. The exhaust flow rate that is required to generate and sustain a pre-selected negative pressure in the mask is a direct measure of the mask leakage flow rate, which can be used as an index of respirator fit.

Phase II objectives included defining inspiratory pressures and flow rates for various air purifying media over a range of metabolic work rates. This information will be utilized to make fit testing more representative by making it work-rate dependent. Phase III will focus on determination of actual workplace respirator fit factors with the negative pressure system.

### Methodology

Sensitivity and precision limits of the constant negative pressure quantitative fit test method were determined in a sequential comparison study using a computerized aerosol fit test system as a comparison standard. A test population recruited from Air Force personnel already assigned to a respiratory protection program was used.

Capabilities of the new method to measure respirator fit over a range of non-rest work rates was examined with a computerized open-circuit spirometric technique. A bicycle ergometer was used to set and maintain 4 different work rates, and inspiratory pressures and flow rates were measured for both male and female subjects wearing half- and full-face air purifying respirators equipped with low, medium, and high resistance cartridges.

### Significant Findings

The negative pressure system, which is non-invasive, proved to be a more sensitive detector of respirator leaks than the aerosol system. It also consistently exhibited less system variation and produced more conservative measures of respirator fit than the aerosol system.

Examination of respirator fit at work rates rather than rest can be accomplished by varying the challenge pressure maintained inside the respirator during the negative pressure fit test. Inspiratory pressure inside the respirator was found to be primarily determined by the parameters of work rate, mask type, and air purification media. A model has been developed that allows the challenge pressure for the negative pressure fit test to be set as a function of these parameters. The result is a

measure of respirator fit that is more representative of what happens as the respirator is actually worn.

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## Faceseal Leak Identification on Half-Mask Respirator

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 Grant Number: *1 R03 OH02580-01*  
 Start & End Dates: *04/01/88 - 03/31/89*  
 Funding Level: *\$18,639 (\$18,639 Cum)*

### Importance to Occupational Safety and Health

The results of this study have both practical and theoretical applications. Knowledge of the association of facial dimensions to leak sites may be useful to respirator program administrators in the selection of an appropriate model of half-mask respirator for an individual. They may also be useful in the design of more effective half-mask face pieces. These results may also contribute to more accurate modeling of respirator leakage. Leak location and shape are critical factors in defining leak flow characteristics, yet they have been the subject of assumptions in prominent leak models.

### Objectives

The purpose of this study was to identify the location and shape of faceseal leak sites on a half-mask respirator. It was also intended to determine if these characteristics were associated with critical facial dimensions of the wearers. It was hypothesized that most leaks would occur around the nose and they would be diffused over a large area of the faceseal.

### Methodology

Leak sites were identified by conducting quantitative fit tests on human subjects with an aerosol of a fluorescent whitening agent. After the fit tests, the respirators were removed and the aerosol deposited at the leak sites was made visible under longwave ultraviolet light. Observed leaks were documented by photographic methods and

classified as to location and one-dimensional shape. Selected facial dimensions of test subjects were measured by standard anthropometric methods. Data were entered on a computer spreadsheet and analyzed by appropriate statistical techniques.

### Significant Findings

Results of this study indicate that about 79% of all subjects wearing a half-mask respirator had face seal leaks at the nose or multiple leaks which included the nose. About 51% of all the subjects had leaks at the chin or multiple leaks which included the chin, while only about 19% had leaks at the cheek or multiple leaks which included the cheek. The distributions of leak sites on male and female subjects were not significantly different.

Approximately 73% of leaks on all subjects were diffuse, although females were found to have a significantly smaller proportion of diffuse leaks than males (63% vs. 82%).

The association of the 12 measured facial dimensions with eight leak site subsets were also tested. Statistically significant associations were found in 24 of the 96 tests. Of the significant dimensions, 75% were smaller than their comparison groups. About 71% of the significant differences were attributed to differences in gender. About 58% of the significant dimensions were face width measurements, about 17% were face length measurements, and about 17% were arc measurements. Of the two dimensions used to define respirator test panels (face length and lip width) only face length was significantly associated with two leak site subsets.

Nose dimensions comprised 25% of the significant associations of facial dimension to leak site category. These results would indicate that nasal dimensions should be considered in defining respirator test panels and in the sizing and selection of respirators for individual wearers.

Based on observed deposition patterns, diffuse leaks were considered to approximate slits, and point leaks to approximate round holes. These shapes would have implications on the leak flow equations used in respirator leak models, and the pressure decay through face seal leaks. Due to the high prevalence (73%) of diffuse leaks, appropriate equations may be those that represent flow through slits rather than round holes.

A significant observation in this study was the presence of very heavy aerosol deposition along air flow streamline patterns on about 22% of the subjects tested. All of these patterns originated from point leaks followed a relatively straight line to the subjects' nostril or mouth, and all but one were nose leaks. Streamlining was hypothesized as

causing bias in the measurement of fit factors in laboratory mannequin studies. This study provides evidence that this phenomenon also occurs on human subjects.

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## An Advanced Respiratory Protective Device

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Program Area: *Respirator Research*  
Grant Number: *5 R44 OH02312-03*  
Start & End Dates: *09/30/86 - 09/14/90*  
Funding Level: *\$199,843 (\$448,419 Cum)*

### Importance to Occupational Safety and Health

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

The presence of an unambiguous signal to warn the user that the cartridge is almost expended would give greater protection to the user, who would not have to rely on sensory indicators, such as smell. In addition, the AESLI could be used for toxic gases for which there is no sensory warning, regulations permitting. This could lead to the use of air-purifying respirators with many compounds which now require the use of a SCBA (self-contained breathing apparatus).

The 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. If AESLI were available, it might be possible to continue to employ air purifying respirators instead of self-contained breathing apparatus (SCBA) in many applications. Simple positive and negative pressure respirators

provide the economic benefits of lower cost and increased productivity, as well as improved safety and comfort for workers.

### Objectives

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

### Methodology

Micro-chemical sensors that operate on ultra low power and detect ppm-ppb 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 SAW micro-sensors are being investigated. The approach is to interface the new micro-sensor technology with existing adsorbent-based protection systems to create a new respiratory protection device that can protect the user and alert/alarm the user when the adsorbent is spent and the protection is not adequate.

### Significant Findings

Micro-watt microsensors that operate at the adsorbent bed temperature have been designed and fabricated. Initial results indicate that it is possible to detect compounds at the ppm range and to predict the exhaustion of a carbonaceous adsorbent bed. A prototype alarm system, with a flashing LED alarm, has been placed in a full face respirator. Tests and evaluations are planned.

### Publications

Stetter JR: U.S. Patent: Application Disclosure in preparation for the "Detection of Vapor Breakthrough in Adsorbent Beds" TRI, 1987

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## Development of Novel Sorbents for Respirators

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Program Area: *Respirator Research*  
Grant Number: *1 R43 OH02698-01*  
Start & End Dates: *09/30/89 - 03/29/90*  
Funding Level: *\$46,820 (\$46,820 Cum)*

### Importance to Occupational Safety and Health

The adsorbent in industrial respirator cartridges is activated carbon. At low relative humidities, water vapor has little effect on the adsorption of most organics in respirator cartridges. However, at a critical relative humidity (usually 50 - 60%), water vapor can substantially reduce both the effective and equilibrium capacity for organics. This is due to capillary condensation of water in micropores in the activated carbon. In dry air, the cartridges are effective in removing non-polar organics of molecular weight above 100. However, current chemical cartridges can be very ineffective at removing volatile, polar organics, such as ethylene oxide or vinyl chloride. The desired result of this project would be an "all purpose chemical cartridge," useful for a wide variety of toxic gases over a wide range of relative humidities. This versatile cartridge would provide substantially improved protection for industrial workers potentially exposed to toxic gases, the composition of which is not necessarily known. The adsorbent would be useful in industrial respirators, military gas masks, and industrial adsorbents.

### Objectives

In this work, a fraction of the pores in the activated carbon will be filled with a low volatility, non-toxic, polar, organic liquid. The light, polar, organic vapor should dissolve in the heavy, polar, organic liquid contained in these pores. The presence of the added organic liquid will not prevent the non-polar or weakly polar organics in the air stream from adsorbing on the surface of the untreated carbon pores. If the heavy organic were not toxic and had a high odor threshold, the very small amount that would escape into the air stream would not harm or annoy the respirator user. The

heavy organic liquid used to dope the activated carbon also could reduce the tendency of water to capillary condense in the adsorbent pores. The overall aim of this project is the development of a sorbent to solve either the problem of inefficient removal of toxic, volatile, polar organics or of decreased efficiency at high humidities.

### Methodology

Two methods will be used to introduce the dopant into the pores of the carbon. First, the dopant will be dissolved in methanol and this mixture added to the carbon. The carbon will be allowed to equilibrate at a slightly elevated temperature, after which the methanol will be removed by evacuating the sample. The second method will be to add the dopant liquid directly to the carbon and anneal the sample at ca. 100°C.

The equilibrium adsorption of toxic organics on modified and unmodified activated carbon will be measured as a function of toxin partial pressure and relative humidity using a gravimetric adsorption apparatus. The equilibrium concentration of the organic toxin in the system will be analyzed on a gas chromatograph.

The organic toxins to be investigated are acetaldehyde, methanol, carbon tetrachloride, and 1,2-propylene oxide. The dopants to be investigated are glycerol, squalene (2,6,10,15,19,23-hexamethyltetracosane) and 1-dodecanol.

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## Human Metabolism of Halothane – Mechanisms of Toxicity

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Program Area: *Other Occupational Needs*  
Grant Number: 5 R01 OH00978-09  
Start & End Dates: 12/01/86 – 06/30/90  
Funding Level: \$281,968 (\$1,849,145 Cum)

### Importance to Occupational Safety and Health

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

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

### Objectives

We are studying three interrelated aspects of the hepatotoxicity of halothane and related halogenated hydrocarbons: First, the mechanism by which metabolism of halothane or dibromoethane causes acute hepatic necrosis by rapid damage to essential cellular proteins; second, the metabolic pathway by which formation of free radical metabolites of these halogenated hydrocarbons leads to peroxidation of cell membrane phospholipids and how some of these peroxidized phospholipids may be converted into potent mediators of inflammation and activators of macrophages; 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<sub>4</sub> (LTB<sub>4</sub>) in liver cells was studied by isolating LTB<sub>4</sub> with high pressure liquid chromatography (HPLC), confirming its structure with desorption chemical ionization mass spectrometry (DCI-MS), and measuring its activity with RIA.

### Significant Findings

The individual contributions 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<sub>4</sub>. This demonstrates that damaged hepatocytes could release powerful chemoattractants, such as leukotriene B<sub>4</sub>, 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.

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## Chromium Distribution and Toxicity in Mammalian Cells

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Program Area: *Other Occupational Needs*  
Grant Number: *5 R01 OH01630-07*  
Start & End Dates: *09/01/87 - 08/31/90*  
Funding Level: *\$150,104 (\$713,490 Cum)*

### Importance to Occupational Safety and Health

Short-range: We are able to detect and quantitate, within hours, the development of toxic injury in single cells and their regional location in liver tissue. Little is known about the initial events following exposure to occupational toxicants.

Long-range: These studies provide an accurate means for quantifying which cells die (or are

injured) and where such cells are located following exposure to an occupational toxicant such as chromate, and how the injury was repaired. These studies should provide a guideline as to what cellular interactions are probable and where they occur during the course of hepatotoxic injury and recovery.

### Objectives

We are conducting a computer-aided microscopy (CAM) study of the 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. To our knowledge, this is the first such report of apoptosis as a feature of Cr(VI) toxicity. We therefore wanted to compare the multi-phasic response of mouse liver to Cr(VI) toxicity, an apoptogen, with the response to CCl<sub>4</sub> toxicity, the putative necrogen. That is, each toxicant will generate a unique multi-phasic response in the liver, as seen in 3 phases of injury: cell injury/death, inflammation, and repair of the liver. Homeostatic mechanisms play a major role in the maintenance of liver; cell loss, via normal attrition or by an injurious agent, results in compensatory mechanisms relating to removal of the effete cells (by the process of inflammation) and cell proliferation to regain the cell mass. Of each of the 3 phases, we will experimentally ask: What cells are affected? When are they affected and what loci in the liver are these changes found?

As we analyze hepatotoxic effects of Cr(VI), we will study the utility of CAM quantitation of histocytochemical images as valid means of assessing toxicity of environmental agents. In particular, we will develop analyses at the high magnification, viz., 40-100x obj. lens, focusing on changes in nuclear textures. Two strategies for enhancing the textural analyses of nuclei will be investigated: the use of fluorescent stains specific for AT bases or GC bases and the use of selective enzymatic removal procedures. We feel that selective "destaining" can be accomplished by endonucleases, RNAses, and proteases to selectively remove nuclear macromolecules, thereby enhancing nuclear textures of liver cells.

### Methodology

The main technique used is the capture of images at the level of the light microscope (LM). With the use of several assays at the level of LM, (viz., fluorescent and non-fluorescent stains, immunocytochemistry, radioautography and *in situ* hybridization), we feel that our CAM system

provides us with a wide range of tissue analysis for identification and quantitation of cells and their contents. We first examined liver response to acute exposure to ip injection of sodium dichromate; response to repeated dose/chronic exposure was then compared to a database on acute response.

### Significant Findings

Several significant features of sodium dichromate (Cr(VI)) hepatotoxicity, *in vivo*, were observed in mice treated with a sub-lethal dose (25 mg/kg). Microscopic analysis of liver sections revealed a distinct pattern in how the hepatic cytoarchitecture changed over a period of 5 days following ip injection. Specifically, a regional (focal) response to insult, apoptosis, was observed in periportal regions but not in pericentral regions. We believe this is the first such report of apoptosis as a feature of Cr(VI) hepatotoxicity. Because these apoptotic cells first occur at the epithelial surface of the liver 6 hours post-injection, but not in controls, we suggest that these apoptotic cells are early signs of contact injury.

This type of apoptosis, i.e., a consequence of toxic injury, contrast with other reports of apoptosis occurring in rat liver during the involution of liver hyperplasia, following lead-induced necrosis or induced by hepatomitogen, cyproterone acetate. In those studies, apoptosis was viewed as part of a homeostatic mechanism, following hyperplasia, rather than an early indication of toxic injury. Our observation that apoptotic phenomena was occurring on a larger scale, appearing as cohorts of apoptotic cells, by 2-3 days following Cr(VI) injection differs from the "classic" definition of apoptosis by Wyllie and Kerr (Intern Rev Cytol 68:251, 1980) that apoptotic cells occur as single cell phenomena. Because the acute hepatic response to Cr(VI) involves both programmed cell death and cell proliferation, such phenomena, repeated on a chronic basis, may eventually lead to "uncontrolled compensatory hyperplasia terminating in neoplasia."

In addition to the early apoptotic response in periportal areas observed, starting about 3 days after chromium exposure an increase in ploidy was observed in all liver regions. This increase was noticeable 6 days after treatment. When we attempted long-term (chronic) studies, we saw no difference between control and chromium-treated animals. Apparently the effect of chromium on ploidy is to increase the normal rate of polyploidization, but not the final ploidy. That is, in short-term studies with young animals, ploidy is increased, but it is still less than that seen among old control animals. We believe that an increase in

the rate of polyploidization may be a generalized response to toxic agents.

Quantitative analysis of Cr(VI)- and CCl<sub>4</sub>-induced injury on liver cell metabolism, indicated by changes in mean OD of Periodic acid-Schiff (PAS)-stained tissue also indicated that the regional pattern of glycogen depletion was different. That is, Cr(VI)-treated mice were depleted in periportal regions and were relatively unaffected in pericentral regions. In contrast, CCl<sub>4</sub>-treated mice showed glycogen depletion in pericentral regions, but not in periportal regions. In addition to the regional glycogen depletion, a uniform depletion at the epithelial edge of the liver section was observed (similar to pattern of apoptotic contact injury observed at the edge). Finally, the degree of glycogen depletion was dependent on the length of toxicant exposure. Maximum depletion was seen at 1 d after CCl<sub>4</sub> treatment and 2 d following Cr(VI) treatment, followed by a gradual return of staining to control levels. Non-parenchymal cells (NPC) appeared at sites of injury only 2 days following Cr(VI) injection (at epithelial surface and periportal areas); we will investigate whether this NPC population were oval cells, or hepatocytic precursors.

### Publications

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## Poison Centers: A Resource for Occupational Health Services

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Program Area: *Other Occupational Needs*  
Grant Number: *5 R18 OH01981-02*  
Start & End Dates: *02/01/87 - 01/31/90*  
Funding Level: *\$165,593 (\$321,937 Cum)*

### Importance to Occupational Safety and Health

Regional poison centers are frequently called upon to provide information regarding potential or actual occupational exposures but often do not have the training or resources to efficiently respond to these requests. The training needs assessment conducted as part of this project is the first national survey of existing training and training needs of poison center staff for occupational health services. The response protocols developed will be of considerable use to poison control centers in efficiently and effectively responding to requests for occupational health information.

### Objectives

This project is designed to determine the usefulness of regional poison control centers as both a disseminator of occupational health information and as an occupational disease surveillance mechanism after suitable training and the development of appropriate response protocols.

### Methodology

The following activities are included in this project:

1. The development of an occupational health training course for poison information specialists of a regional poison center and evaluation of its use by the Cincinnati Drug and Poison Information Center staff (DPIC);
2. The development of model protocols for use by poison center occupational health specialists in responding to requests for information about specific dangerous chemical substances in the workplace. An evaluation of existing

information sources, both printed and computerized, will identify the useful toxic substances management and prevention protocols to be used in the development of a uniform information and response system for poison center staff;

3. Occupational health professionals will assist the poison center to maximize the impact of these activities on the dissemination of quality information to the public;
4. The design of occupational health data sheets for use by the poison center for the collection of uniform data on each request and the quality of service provided by the poison center staff will be evaluated by an industrial hygienist and occupational physician; and
5. An evaluation of these data for their value as a surveillance method for the detection of occupational disease.

### Significant Findings

In an evaluation of telephone responses to 185 occupational health inquiries received after poison staff had undergone training, almost two-thirds were handled using information sources: the Poisindex System, Chemical Hazards in the Workplace, and Occupational Health Guidelines for Chemical Hazards. In 70% of these cases, help from an environmental toxicologist or occupational medicine resident was also utilized in the response. Almost one-half of the inquiries were handled within 15 minutes each.

### Publications

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## Plasma Proteins: Markers of Chemical Exposure

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Program Area: *Other Occupational Needs*

Grant Number: *5 R01 OH02149-04A1*

Start & End Dates: *01/01/86 - 06/30/89*

Funding Level: *\$92,701 (\$286,290 Cum)*

### Importance to Occupational Safety and Health

The purpose of this study is to develop biological markers of chemical exposure. The chemical and biological assays thus developed to measure changes in plasma proteins can be used to monitor occupationally-exposed populations. Correlation between the changes in plasma proteins

and the medical histories of the occupationally-exposed individuals can be used for medical surveillance as well as for risk assessment.

### Objectives

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

### Methodology

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

### Significant Findings

The *in vitro* inactivation by three epoxides and two dihaloethanes of the proteinase inhibitory activities of  $\alpha_1$ -proteinase inhibitor ( $\alpha_1$ -PI), as well as those of the plasma itself, was investigated. Each of the three epoxides (styrene oxide, ethylene oxide, and propylene oxide), inactivated the elastase inhibitory or trypsin inhibitory activity of the proteinase inhibitor, as well as that of whole plasma. Styrene oxide was the most effective inactivator of either purified  $\alpha_1$ -PI or plasma, followed by ethylene oxide and propylene oxide in a decreasing order of potency. The dihaloethanes, 1,2-dichloroethane and 1,2-dibromoethane, also inactivated the proteinase inhibitory activities of  $\alpha_1$ -PI, with the former being somewhat more effective than the latter. Concomitant loss of the amino group was also observed with these chemicals, and in most cases it correlated well with the decrease in  $\alpha_1$ -PI activity. Since the loss of  $\alpha_1$ -proteinase inhibitory activity in the lung has been proposed as a key factor in causing pulmonary emphysema and since cigarette smoke causes pulmonary emphysema, we also studied the effects of aldehydes (acrolein, glyoxal, and pyruvic aldehyde) and ketones (2,3-pentadione

and 2,3-butadione) found in cigarette smoke on  $\alpha_1$ -PI activity. Acrolein was found to be the most potent inactivator, followed by pyruvic aldehyde and glyoxal, while 2,3-pentadione and 2,3-butadione were virtually ineffective. These studies indicate that  $\alpha_1$ -PI can be inactivated by non-oxidative processes. We have shown that acrolein inactivates  $\alpha_1$ -PI through the modification of lysine and histidine residues. We have demonstrated the synergistic inactivation of  $\alpha_1$ -PI by mixing aldehydes (acrolein or pyruvic aldehyde) with industrial chemicals (styrene oxide or 1,2-DCE) and vice-versa. The data obtained from these studies suggest that smokers exposed to chemicals in industry may be more prone to lung emphysema due to synergistic inactivation of  $\alpha_1$ -PI by chemicals and cigarette smoke components.

The possibility of using glutathione S-transferase (GST) of red blood cells as a marker of chemical exposure was also explored. These studies were conducted with purified GST isolated from human erythrocytes as well as in red blood cells. Acrolein, styrene, propylene, and ethylene oxides (1,2-DBE, and 1,2-DCE) each caused a dose-dependent inhibition in the activity of GST, using 4-chloro-2,6-dinitrobenzene as a substrate, raising the possibility of using GST as a marker of chemical exposure.

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## Dose/Response for Occupational Styrene Exposures

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Program Area: *Other Occupational Needs*  
 Grant Number: *5 R01 OH02221-02*  
 Start & End Dates: *09/29/86 - 03/31/89*  
 Funding Level: *\$135,524 (\$259,214 Cum)*

### Importance to Occupational Safety and Health

The project represents one of the first comprehensive applications of biochemical epidemiology to an occupational cohort. The extensive exposure assessment, performed longitudinally, minimized problems involving bias and the associated misclassification which are typically encountered. This study design has allowed us to detect elevated levels of SCEs at styrene concentrations below those which had heretofore been reported. The development and application of methods for detecting styrene-7,8-oxide (SO) adducts of DNA (SO-DNA) and hemoglobin (SO-Hb) will produce important new information concerning the bioavailability of SO in humans exposed to styrene.

### Objectives

This study is investigating the linkages between exposure, uptake, and genotoxic response resulting from occupational exposure to styrene in the reinforced-plastics industry. A longitudinal assessment of exposure was completed in which 48 subjects were monitored in a single facility where fiberglass boats were manufactured. The primary purpose of the study is to accurately estimate the airborne exposure and uptake of each individual in the cohort for comparison with several indices of genotoxic response measured in blood samples, i.e., sister-chromatid exchanges (SCEs) in peripheral

lymphocytes and the adducts, SO-Hb and SO-DNA. This would allow exposure-dose-response relationships to be established for styrene and for SO arising from metabolism of styrene *in vivo*. A secondary objective is to correlate the above indices of styrene uptake and genotoxicity with each other in a common pool of samples where exposure had been carefully documented.

A separate aspect of the investigation concerned the application of a pharmacokinetic model for styrene, derived under constant-exposure conditions, to the situation typical of occupational exposures where air levels vary greatly over time. The objective of this investigation was to determine the extent to which tissue concentrations of styrene in these compartments were damped compared to the air levels.

### Methodology

Each individual's airborne exposure was measured 7 times (shift-long sampling), his/her blood was collected 4 times, and his/her exhaled air was collected up to 25 times over a 12-month period. Exposures were measured with passive monitors employing coconut carbon. Measurement of styrene in the exhaled air employed a new device which collects styrene from 3 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. SO-DNA is to be measured by a modification of the <sup>32</sup>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. Concerning the numerical analysis, the input to the pharmacokinetic model was a lognormally-distributed, autocorrelated series of exposure concentrations while the output consisted of the resulting concentrations of styrene in the central and peripheral compartments.

### Significant Findings

The exposure assessment was completed with analysis of styrene in all samples of air, exhaled air, and blood. Individual mean exposures ranged between 0.2 and 55 ppm for the 48 subjects with an overall mean of 15.1 ppm. There was a strong linear correlation between the styrene concentrations in exhaled air and blood ( $r^2 = 0.79$ ,

n = 109), indicating that the method of exhaled-air measurement is predictive of the uptake of styrene in the body. The relationship between the mean exhaled-air concentrations/subject and shift-long exposure/subject also showed a strong linear correlation ( $r^2 = 0.76$ , n = 48); this indicates that differences in individual rates of uptake, which might arise from skin contact, respirator use, or differences in physiological parameters, were relatively minor.

SCEs have been scored from two of the four sets of blood samples. Preliminary results suggest that styrene exposure was significantly correlated with the number of SCEs/cell ( $r^2 = 0.211$ , p = 0.0001, n = 48). This indicates that styrene exposure below 50 ppm contributed to elevated SCEs; such findings of SCEs at these levels of styrene exposure have not been reported before.

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

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

Results of numerical simulations employing the pharmacokinetic model suggest that the burdens of styrene in the central and peripheral compartments are likely to be highly damped compared to the air concentrations. The coefficients of variation of the series of burdens varied between about 30-50% of that associated with exposure (averaging time = 15 min) in the central compartment and between about 10-20% of CVc in the peripheral compartment.

A renewal application has been submitted which requests support to measure SO-Hb and SO-DNA, as well as other dose indices, in the blood samples.

#### Publications

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Liu SF, Rappaport SM, Pongracz K, Bodell W: Detection of Styrene-Oxide DNA Adducts in Lymphocytes of a Worker Exposed to Styrene. In *Methods for Detecting DNA-Damaging Agents in Humans, Applications in Cancer Epidemiology and Prevention*, (eds. H Bartsch, K Hemminki, IK O'Neill), IARC Scientific Publications No. 89, Lyon, pp 217-222, 1988

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## Artificial Intelligence Occupational History

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Program Area: *Other Occupational Needs*  
Grant Number: *5 R01 OH02288-02*  
Start & End Dates: *05/01/87 - 04/30/90*  
Funding Level: *\$141,724 (\$248,018 Cum)*

### Importance to Occupational Safety and Health

Occupational Health (OH) expertise is not universally available to all workers and investigators who require it. The training deficits in OH are greater than in many other areas of medicine. Artificial Intelligence (AI) techniques can help meet the need by providing some of the professional expertise, including both knowledge and inference process, by computer. AI is significantly different from database or decision tree methods which have been used in the past. These methods are likely to be particularly valuable in providing expertise to non-OH clinicians for the recognition of occupational disease and for population surveillance.

### Objectives

The project seeks to develop and validate an AI based expert system for the recognition of occupational lung disease. While the focus is on

occupational lung disease, the project is developing methods which may be directly applicable to many other areas of occupational disease. Rather than working within the constraints of general purpose commercial AI shells, the project is developing an OH specific system.

### Methodology

The artificial intelligence occupational history system (AIOHS) is an expert system being developed specifically for these goals. It has several functional features: (1) Inheritance (application of general principles to more specific instances); (2) Predicate calculus (ability to deal quantitatively with uncertainties in general knowledge or case-specific data); (3) Non-monotonic knowledge base (can handle apparently conflicting information); (4) Incremental growth (can add new information as it is found without restructuring); (5) Selectivity of data acquisition (only asks for information when relevant); (6) Explanation (can explain why it reaches certain "diagnoses"); (7) Shafer-Dempster model for handling case specific information; (8) Flexibility of relationships (relationships among objects of interest, defined below, are not constrained by a monotonic hierarchical system such as SOC); and (9) Includes features technically described as frames-slots, defaults, perspective, and hybrid forward-backward chain logic.

The inference engine (system to manipulate information to apply general knowledge to specific cases) was developed in C. The knowledge base (general information) was developed in a commercial relational database (dBase) and then compiled into the more efficient C compatible format.

Two user interfaces are available—a highly efficient C based interface and a very "user friendly" dBase system.

An extensive "knowledge editor" is being developed to facilitate addition of knowledge to the system, incorporating extensive checking to assure compatibility and facilitate system development by professionals without AI specific experience.

The AIOHS is currently undergoing field trials in several clinical settings to determine its feasibility, the number and types of diseases it suggests, the relevant exposures it suggests which were otherwise not evident, and the acceptance by non-OH clinicians.

### Significant Findings

Conduct of this project thus far has suggested that development of a system of sufficient size to be useful is a complex but feasible process. A structure was developed to hold all relevant knowledge in two types of structures: Primary objects hold information about the nature of a specific object (job, industry, agent, or disease). Relations rules describe pairwise relations between objects of the same type (e.g., Job A is a subset of Job B) or different types (e.g., agent A causes disease B). An inference engine has been developed to apply this general knowledge to case-specific information to suggest reasonable diagnostic possibilities which should be considered by the clinician or collected for surveillance purposes. This takes into account uncertainties of knowledge as well as factors such as estimated dose, threshold, duration, latency, and baseline disease prevalence.

Experience with this project also demonstrated that the complexity of knowledge base development and modification (e.g., based on initial field trials) increases considerably as its size grows. Hence, while *a priori* methods were adequate for development with a relatively small number of rules, a more structured knowledge editor, built specifically for OH, has been developed.

Initial field use shows that the system can suggest relevant exposures and possible occupational diseases which would not necessarily have been otherwise detected.

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## Fast-GC for Industrial Hygiene Monitoring/Analysis

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Program Area: *Other Occupational Needs*  
Grant Number: *5 R01 OH02303-02*  
Start & End Dates: *09/29/86 - 03/31/89*  
Funding Level: *\$95,360 (\$211,263 Cum)*

### Importance to Occupational Safety and Health

Real time air monitoring is central to:

1. evaluating airborne workplace hazards prior to the design, installation, and/or operation of process changes or control devices;
2. detecting sudden releases of toxic air contaminants to the workplace or the community;
3. evaluating suspected air contaminant-related adverse health effects during epidemiologic studies; and
4. conducting health hazard evaluations.

This project is aimed at developing the methodology for the rapid, direct monitoring of airborne contaminants using gas chromatographic (GC) techniques. Since methods that are presently available for this application are quite slow, this new instrumentation will assist in the achievement of all of the above health-related goals.

### Objectives

A prototype system will be designed, constructed, and evaluated for repetitive, high-speed workplace air monitoring. High speed will be defined as 5-15 seconds per analysis.

### Methodology

1. Model the optimal design conditions for the highest possible chromatographic resolution attainable in 5-15 seconds.
2. Construct a prototype GC instrument, including optimized inlet system and system electronics.

3. Evaluate the system for speed, precision, accuracy, resolution, and limit of detection for target analytes of industrial hygiene significance.

### Significant Findings

- (Components of the system that initially appeared simple actually required very large inputs of effort to develop. Examples of this are the capillary tube cold trap itself, and the high speed electrometer.)
2. The system has been fully validated for benzene, toluene, and xylene, and partially tested for chloromethane. Precision and accuracy were better than that achievable using standard GC methodology. Chromatographic analysis time was <10 seconds per sample, an improvement in speed of over 60 fold. There was no effect of humidity between 20% and 80% used in the evaluations. (Evaluation of additional target analytes is in progress.)
  3. Design features have been defined for further development, such as software needs for continuous monitoring applications, configuration requirements for portable use, and detector requirements for trace chlorofluorocarbon monitoring. (Work will continue with EPA support.)

### Publications

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## Hydrocarbon Exposure and Chronic Renal Disease

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Program Area: *Other Occupational Needs*  
Grant Number: *1 R01 OH02391-01A2*  
Start & End Dates: *09/15/89 - 09/14/92*  
Funding Level: *\$182,003 (\$182,003 Cum)*

### Importance to Occupational Safety and Health

Occupational exposure to nephrotoxins has for many years been suggested as an important etiological factor in chronic renal failure. However, only a few epidemiologic studies have attempted to clarify this suspicion. There is little doubt that chronic tubulointerstitial nephropathy may result from heavy metal toxicity; however, this 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), 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 two major counties in Oklahoma. Cases will include all adult patients between the ages of 18 and 79 with chronic renal disease (both those with ESRD and those not yet at that stage) having a confirmed diagnosis of idiopathic chronic

glomerulopathy (ICG) as their primary disease and patients with chronic renal failure who have an unknown primary disease. Minimum criteria for diagnosis of ICG will include either a histologic diagnosis or the presence of unexplained proteinuria exceeding 2 gms/24 hrs. All new cases diagnosed between January 1, 1985 and July 31, 1992 meeting these criteria will be included in the study.

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

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

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

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

### Significant Findings

At the present time, the effort has gone into the development of instruments and protocol for Random Digit Dialing, hiring/training of personnel, logistics, and arrangements with hospitals and a nephrologist. Interviews are expected to begin in January, 1990. Therefore, there are no significant findings to report at this time.

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## Self-Training, Self-Optimizing Infrared Expert System

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Program Area: *Other Occupational Needs*  
Grant Number: *5 R01 OH02404-02*  
Start & End Dates: *09/29/87 - 12/31/89*  
Funding Level: *\$114,857 (\$238,744 Cum)*

### Importance to Occupational Safety and Health

Real time air monitoring is central to:

1. evaluating airborne workplace hazards prior to the design installation, and/or operation of process changes or control devices;
2. detecting sudden releases of toxic air contaminants to the workplace or the community;
3. evaluating suspected air contaminant-related adverse health effects during epidemiologic studies; and
3. conducting health hazards evaluations.

This project is aimed at developing the methodology for the rapid, direct monitoring of airborne contaminants using Fourier transform infrared (FTIR) spectroscopy, and to the developing of the software to allow the use of the method by industrial hygienists. As such, this new instrumentation will assist in the achievement of all of the above health-related goals.

### Objectives

A self-training, self-optimizing expert system will be developed to identify the components of mixtures of airborne contaminants of industrial hygiene significance using infrared spectroscopy.

### Methodology

1. Acquire a library of the IR spectra of organic vapors and gases of significance to industrial hygiene at certified concentrations in air.
2. Determine the spectral regions for optimal specificity and limit of detection for each

compound separately and in mixtures likely to be found in workplace air.

3. Develop optimal software for the quantitation of the components of mixtures of organic vapors in air.
4. Develop optimal software for the identification of the components of mixtures of organic vapors in air.
5. Develop the expert system and self-diagnosing software tools for the use of the above system by an industrial hygienist.
6. Work with NIOSH and the EPA-Environmental Response Team for evaluation of FTIR applied to actual air samples.

### Significant Findings

1. Objectives 1-3 (above) have been accomplished and published. Quantitation of workplace samples from both semiconductor device manufacturing processes, and degreasing operations in metal manufacturing, have been accomplished. The latter study was performed in conjunction with the evaluation of a Foxboro MIRAN for use in the quantitation of air contaminants. In addition, a method was validated for the quantitation of CS<sup>2</sup> eluates of charcoal tubes by FTIR for this application.
2. Objective 4 has just been accomplished, and is in the process of being automated. We had consistently failed to accomplish this objective using expert system techniques. An algorithmic method, iterative least squares fitting (ILSF) has been utilized to accomplish this objective. ILSF must now be evaluated for actual workplace air samples.
3. The above system development was accomplished on a Nicolet 1280 mini-computer using Fortran 77 language. All of the data and software is being transferred to an MS-DOS 80386/387 system, with software re-written in "C" and "CLIPS" for computing speed and flexibility. Microsoft Windows is being used as an interface between the software and the industrial hygienist. Initial improvements in speed of a factor of approximately 50 have been realized thereby. Work will continue with support from G.M. Co.

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## Halogenated Hydrocarbon Toxicity in Proximal Tubules

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Program Area: *Other Occupational Needs*  
Grant Number: 5 R01 OH02417-03  
Start & End Dates: 09/01/87 - 08/31/90  
Funding Level: \$93,942 (\$279,085 Cum)

### Importance to Occupational Safety and Health

Chloroform and carbon tetrachloride are environmental and occupational contaminants with documented nephrotoxic potential in humans and laboratory animals. The primary site of kidney

damage produced by these solvents is the proximal tubule.

This research project explores the toxicity of chloroform and carbon tetrachloride using proximal tubules from rabbits and humans and examines prospective *in vitro* methods for studies of nephrotoxicity. The anticipated useful information to come from this project will (1) further development of meaningful predictive *in vitro* toxicology methods using rodent and human tissues, and (2) enhance understanding of the mechanisms by which these organic solvents cause kidney damage.

### Objectives

The overall aims of the project are to examine (1) the validity of the isolated rabbit tubule model as a tool in the study of nephrotoxicants, and (2) the validity of the rabbit tubule model as a predictor of nephrotoxicity in humans.

### Methodology

Kidney proximal tubules are isolated from control and phenobarbital-induced rabbits by non-enzymatic sieving techniques and then studied *in vitro*. Such tubules in suspension are used to (1) describe the concentration and time dependence of the solvent-induced damage during short-term incubations, (2) evaluate the role of cytochromes P-450, lipid peroxidation, and glutathione in determining the severity of damage to the tubules *in vitro* and (3) be a source of material for studies of various enzyme systems involved in the biotransformation of these organic solvents.

Human kidneys unusable for transplantation are used to develop isolation techniques for human kidney tubules and proximal tubule cells. Human kidney tissue used to examine (1) viability of these human cells *in vitro* (including tissue culture), (2) enzyme activities of potential toxicologic significance, and (3) the usefulness of human kidney cells *in vitro* in studies of organic solvent toxicity.

### Significant Findings

Rabbit kidney proximal tubules were readily obtained in good yield and high purity from both control and drug-treated animals. The tubules in suspension are viable for up to 8 hours. When exposed *in vitro* to chloroform or carbon tetrachloride, tubules demonstrated both a concentration and time-dependent loss of viability as assayed by release of lactate dehydrogenase (LDH). Unfortunately, loss of LDH activity occurred at solvent concentrations too high to be of relevance to

most human exposures. None of the other potential indices of cell viability (organic acid secretion, oxygen consumption, and release of membrane bound enzymes) examined to date are more sensitive than LDH release. Solvent-induced cell damage was confirmed by electron microscopy. Tubules from the phenobarbital-treated animals were no more sensitive to solvent-induced toxicity than the tubules obtained from non-treated animals. Although the tubules accumulated glutathione (GSH) *in vitro*, solvent-induced release of LDH was not appreciably altered by pre-loading the cells with GSH.

When human kidneys were used, neither purely mechanical nor a combination of mechanical and enzyme digestion procedures yielded sufficient quantities of viable tubule segments. In an attempt to obtain tubules from kidneys with less connective tissue, kidneys from two patients with polycystic kidney disease (PKD) were used; only microdissection or enzyme digestion with mechanical stress gave tubule segments. These segments and cells were subsequently identified as being from collecting tubules. Thus, large scale use of isolated human kidney tubules is unlikely to be successful. The use of tissue cultured cells may provide a better approach to the study of long-term, low concentration exposures to organic solvent toxicity.

In this regard, human kidney cortex exhibited 6-9 nMoles GSH/mg protein; rabbit kidney cortex and isolated tubules exhibited 10-15 and 4-7 nMoles GSH/mg protein, respectively. In tissue culture, the rabbit proximal tubule exhibited 3-5 nMoles GSH/mg protein. Cultured tubule cells exhibit stubby microvilli and tight junctions. Confluent cell cultures exhibit an electrical resistance and specific lectin staining consistent with retention of at least some aspects of proximal tubule structure and function. Thus, cultured proximal tubule cells may represent a possible alternative to animal use.

#### Publications

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## Effects of Job Hazards, Health, Incentives on Absenteeism

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Program Area: *Other Occupational Needs*  
Grant Number: *1 R01 OH02586-01*  
Start & End Dates: *09/29/87 - 12/31/88*  
Funding Level: *\$28,147 (\$28,147 Cum)*

### Importance to Occupational Safety and Health

The results of this study will be valuable to business executives and policy makers who would like to reduce absenteeism in the workplace. For an individual firm, reduction of job hazards may entail resources to be drawn from wages in order for workers to work in a safer environment but at a reduced rate of pay. However, a reduction in hazards may result in an increase in productivity, for example, from the reduction in absenteeism. An increase in productivity could, in turn, result in more profits available for higher wages. It, therefore, becomes necessary to identify particular job hazards that would be the least expensive to reduce and provide the business with the greatest reduction in absenteeism.

### Objectives

The University of Michigan's 1972-73 and 1977 waves of the Quality of Employment Surveys (QES73, QES77) of roughly 1,500 randomly selected full-time U.S. employees will be used for the following objectives. (1) The QES77 data tape contains information on 17 possible job hazards and 34 possible injuries or illnesses that in the respondent's view were caused or made more severe by the job. The 17 possible hazards and the 34 illnesses and injuries will be ranked based on their relationship to number of days absent. (2) The QES73 data tape contains information on respondents absences within the past two weeks. Treating absence responses as a dependent variable, Tobit regressions, which are especially designed for truncated, non-normally distributed dependent variables, will be constructed to assess the importance of a variety of independent variables in

explaining absenteeism. Independent variables will include: occupational mortality rates, wages, availability of sick leave, moonlighting, local unemployment, work hours schedule, unionization, marital and family status, spouse's income, age, race, sex, education, commuting distance, amount of overtime, job satisfaction, subjective evaluation of health, presence of back pain, sleep problems, feelings of fatigue and nervousness, obesity, and smoking. (3) An assessment will be made of the relative importance of job hazards in explaining absenteeism, holding constant other independent variables mentioned above. (4) The Tobit statistical model, which is much better suited to explaining days absent than multiple regression, will be discussed with advantages and disadvantages noted.

### Methodology

Three methods will be used: (1) Percentages of persons complaining of various job hazards and injuries by occupation will be tabulated. (2) Tobit regressions will be used to explain fluctuation in self-reported absences with the independent variables mentioned in objectives 2 and 3. (3) The research will consider alternative methods for assessing the importance of an independent variable in a regression which will make use of elasticity, a concept borrowed from economics.

### Significant Findings

1. Measures of job hazards were more important than personal characteristics such as age, race, gender, and schooling, and other job conditions such as overtime, wages, and commuting distance in predicting absenteeism.
2. Insomnia appeared to be a powerful predictor of absenteeism, yet few studies have considered links between insomnia and absenteeism.
3. Back injuries, fractures, colds and flu, strains, and falls lead the list of respondent reasons for their absences.
4. Stress, noise, dust, and dangerous machines were top job characteristics workers identified as causing or contributing to illnesses or injuries.
5. Most economic studies overstate the extent to which "the market" rewards people on dangerous jobs with higher wages because workers lack information on job hazards.
6. Empirical associations between high wages and high job-related death rates appear to be much stronger outside of manufacturing industries. The general association found between high wages and dangerous jobs economy-wide may be overstated due to the inclusion of unique

industries such as mining, construction, and transportation.

7. Back pain is most strongly associated with farmers, service workers, operatives, persons with few years of schooling, low wage work, physically demanding jobs, height, older ages, and smokers.
8. Direct empirical associations were found between workers' time spent striking and industries' injury and illness rates.
9. Unemployment was found to have two opposing effects on highway fatalities. On the one hand, increased unemployment would be associated with lower income and, consequently, less driving since income and driving are known to be positively related. Less driving leads to fewer highway crashes and deaths. On the other hand, unemployment leads to increased stress and decreased ability to concentrate among the unemployed. The stress and poor concentration hypothesis would therefore suggest that increased unemployment would result in increased crashes and fatalities.

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## Permeation of Glove Materials by Organic Solids

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Grant Number: *1 R01 OH02651-01*  
Start & End Dates: *06/01/89 - 05/31/91*  
Funding Level: *\$49,809 (\$49,809 Cum)*

### Importance to Occupational Safety and Health

The exposure of unprotected hands to solid organic chemicals can result in various injuries via dermal absorption. Glove materials used to protect the skin from direct contact may allow the chemicals to permeate, creating conditions hazardous to human health. To provide optimum worker protection, methodology must be developed to evaluate the critical permeation characteristics of breakthrough time, steady-state permeation rate, and steady-state permeation time. By evaluation of a representative set of chemicals, glove materials, and exposure conditions, it should be possible to determine what effect chemical vapor pressure and relative solubility have on the permeation characteristics. Furthermore, the availability of this information will aid in selection of optimum gloves and development of improved glove materials.

### Objectives

The objectives of this study are to develop a method for the evaluation of the permeation behavior of five protective glove materials when exposed to organic compounds using a representative set of 13 chemicals. Variations in this behavior will be evaluated over a range of from 0 - 40°C using material thicknesses of from 0.15 - 0.6 mm. This information will then be related to the vapor pressures for the materials and the relative glove/chemical solubilities. This information should aid in predicting the effective protection for unevaluated glove/chemical pairs. Permeation will also be evaluated over a range of humidities and with simulated perspiration as the collecting medium to more accurately reflect actual exposure conditions.

### Methodology

A glove sample of known thickness is placed between two halves of a permeation cell. A helium flow is directed through one side of the cell, then through a gas sampling loop on a 10 port valve, and then to a flame ionization detector of a gas chromatograph. After a stable detector baseline is observed, a pellet of the chemical to be evaluated is placed in contact with the outer surface of the membrane and the detector response monitored and stored on computer. The response curve is monitored and when steady state has been reached, the position of the valve is changed, which effects an injection of the chemical on to a chromatographic column. The resulting peak is quantified by comparison to a standard and then related to the response at the time of injection for the permeation curve. This allows for the determination of the steady-state permeation rate (SSPR) and detection limit at breakthrough. Breakthrough time is determined based on the first observation of a response greater than twice the signal to noise ratio with no return below the base line. The effect of temperature on SSPR is evaluated by placing the permeation cell in the chromatographic oven. Through the use of a CO<sub>2</sub> cryogenic cooler, temperatures over a range of from 0 - 40°C can be produced with +/- 0.1°C accuracy. Steady state is initially achieved at the upper temperature limit, and the effect of temperature determined by evaluating variations in response while cooling the cell using a temperature ramp of -0.1°C / min.

### Significant Findings

The permeation cell has been constructed and the general method evaluated. A Hewlett-Packard 5890 series II gas chromatograph equipped with an FID detector, 10 port sampling valve, and cryogenic cooler has been interfaced to the cell using a 200 cm heated transfer line. Data collection and analysis is accomplished using a Hewlett-Packard Pascal GC ChemStation, and procedures have been written using the system's macro language to aid in the interpretation of permeation curves. To date, room temperature evaluation of single thickness (5 mil) of latex has been evaluated using chemicals at least in triplicate. These results are summarized below where BT = breakthrough time, SST = steady-state response time, and SSPR is the steady-state response rate in units of  $\mu\text{g}/\text{min}/\text{cm}^2$  when exposed to latex:

Chemical	BT	SST	SSPR
phenol	10.4	80	1.35
p-dichlorobenzene	4.2	50	7.26
naphthalene	4.3	151	0.99
1,4-benzoquinone	8.5	35	1.79

Comparison of SSPR calculated as moles/min/cm<sup>2</sup> with literature values for pressure indicate that the two are related. Insufficient data have been collected to quantify this relationship or to allow evaluation of BT and SST as a function of vapor pressure or solubility.

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## Selective Real-Time Detection of Olefin Gases and Vapors

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Program Area: *Other Occupational Needs*  
 Grant Number: *1 R01 OH02663-01*  
 Start & End Dates: *09/01/89 - 08/31/92*  
 Funding Level: *\$95,489 (\$95,489 Cum)*

### Importance to Occupational Safety and Health

The prototype personal monitoring instrument to be developed during this project will facilitate the collection of more accurate and complete exposure data for each of the target olefin gases and vapors. The chemicals chosen for study have been associated with carcinogenic, neurotoxic, and/or adverse reproductive health effects. Due to the presence of other organic-vapor contaminants in industrial settings where these chemicals are used, real-time measurement of airborne concentrations with current personal direct-reading instruments is often not possible. The sensitivity and selectivity provided by the proposed instrument will enhance efforts to assess and control occupational exposures to these chemicals.

### Objectives

The goal of this research is to develop a prototype instrument for selective real-time measurement of each of a series of olefin gases and vapors in the presence of common olefin and non-olefin industrial co-contaminants. The primary focus will be on the detection of acrylonitrile, butadiene,  $\beta$ -chloroprene, ethyl acrylate, styrene, vinyl chloride, and vinylidene chloride, although data relevant to monitoring other toxic olefins will also be obtained. The instrument will employ a coated surface-acoustic-wave (SAW) oscillator as the sensing element. Selectivity for a given target olefin will be achieved by coating the sensor surface with one of several regenerable trapping agents.

### Methodology

A series of trapping agents will be synthesized and tested for reactivity with each of the target olefins. The trapping reagents will comprise several platinum-olefin coordination compounds of the general formula trans-PtCl<sub>2</sub> (amine) (olefin), and related polymer-bound compounds, designed to react (via substitution of the initially bound olefin) specifically with the target olefin. Subtle changes in the electronic and steric properties of the amine and olefin ligands in the reagent should allow for optimization of selectivity toward each of the target olefins in the presence of other potentially interfering chemicals. It is expected that post-exposure regeneration of the original trapping reagents will be possible *in situ* by simple chemical treatment.

The coated-SAW device will be made with a thin-film heating element to precisely control the sensor temperature. The sensor 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, including sensitivity, selectivity, response time, dynamic range, ambient temperature and humidity effects, and multiple exposure/regeneration cycling.

### Significant Findings

Real-time measurement of styrene vapor has been achieved using a 30-MHz SAW sensor coated with a mixture of trans-PtCl<sub>2</sub> (ethylene) (pyridine) and polyisobutylene. Absorbed styrene vapor displaces ethylene to form the stable styrene-substituted complex, trans-PtCl<sub>2</sub> (styrene) (pyridine), causing a decrease in the oscillator

frequency from the increase of mass on the surface of the sensor. The response exhibits an Arrhenius temperature dependence with calculated detection limits of 3 and 0.6 ppm for operation at 25 and 40°C, respectively. For short-term exposures, there is a linear relationship between the logarithm of the rate of frequency change and the logarithm of the styrene vapor concentration, consistent with a power-law kinetic model for the heterogeneous trapping reaction. Deviation from this behavior observed above 300 ppm at 25°C is attributed to the onset of multilayer adsorption of styrene at the surface of the trapping reagent. No effect on the response to styrene is observed upon simultaneous exposure to each of several olefin and non-olefin solvent vapors used with styrene in industrial processes. Butadiene, however, presents a reversible negative interference by successfully competing with styrene for reaction with the trapping agent. The sensor response exhibits a moderate positive humidity dependence. Following exposure to styrene, the original complex can be regenerated by exposure to ethylene gas, permitting repeated use of the sensor.

3. evaluating suspected air contaminant-related adverse health effects during epidemiologic studies; and
4. conducting health hazard evaluations.

A Fourier transform infrared (FTIR) spectrophotometer equipped with remote sensing (ROSE) optics could be used for a new approach to workplace monitoring. This system would give rapid results for qualitative and quantitative analysis of many gas and vapor mixtures in workplace air and would have few of the problems associated with traditional sampling devices. This system could be configured for transportable use, or for use as a multi-work station fixed monitor.

The relevance of the long-path measurement to personal exposures has not been investigated in the past, but it presents the interesting possibility of tailoring beam geometry to the mobility pattern of workers and thereby acquiring exposure estimates which, because of the spatial averaging characteristic of the measurement, will more closely approximate personal exposures than that normally achieved using fixed-position area monitors.

Thus, this investigation will assist in the achievement of all of the above health-related goals.

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## Theory and Evaluation for a Workplace FTIR-ROSE Monitor

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Program Area: *Other Occupational Needs*  
Grant Number: *1 R01 OH02666-01*  
Start & End Dates: *09/01/89 - 08/31/92*  
Funding Level: *\$148,575 (\$148,575 Cum)*

### Importance to Occupational Safety and Health

Real time air monitoring is central to:

1. evaluating airborne workplace hazards prior to the design, installation, and/or operation of process changes or control devices;
2. detecting sudden releases of toxic air contaminants to the workplace or the community;

### Objectives

1. Measure the effect of heat and humidity on the baseline signal of the FTIR-ROSE system, and on the ability of the system to quantitate individual gases, vapors, and mixtures.
2. Compare and contrast results obtained with the FTIR-ROSE with traditional personal and area monitoring results in an exposure room. (Conditions of air flow rate and turbulence will be systematically varied while the concentration of airborne contaminants emitted from simulated work stations will be measured using the FTIR-ROSE and traditional area and personal monitors.)
3. Develop a model for the use of the FTIR-ROSE, and all optical beam systems, for workplace air monitoring.

### Methodology

The principle focus of this project will be on the experiments in the exposure room at the University of California-Berkeley. This room will be equipped with FTIR-ROSE and with an array of 12 fixed sample points for use with an additional monitoring system. Since the turbulence, air flow rate and vapor concentration in this room can be measured and controlled, a correlation between results obtained by the FTIR-ROSE and the other

monitoring methods can be established for simulated work stations. Evaluation of the results thereby obtained will lead to the establishment of a model for the use of the FTIR-ROSE, and for other beam systems, as workplace air monitors.

### Significant Findings

This project has just started. However, experimental procedures for objective 1 have been completed in an exposure chamber at General Motors Co., covering the range of temperatures and humidity from approximately 10°C to 35°C, and from 0% RH to 85% RH, and for ozone, methanol and a three-component mixture of organic solvents. Data have not yet been evaluated.

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## Peripheral Markers of Muscarinic Receptors

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Program Area: *Other Occupational Needs*  
Grant Number: *5 K01 OH00054-03*  
Start & End Dates: *09/29/86 - 03/31/90*  
Funding Level: *\$32,300 (\$97,100 Cum)*

### Importance to Occupational Safety and Health

These studies are providing relevant data on the characteristics of muscarinic receptors on lymphocytes and on their modulation by cholinergic agents. The finding that similar alterations can be detected in brain and lymphocytes of animals exposed to cholinergic agents and to organophosphorus pesticides suggests that these peripheral measurements might be useful for monitoring alterations of the cholinergic system in solid tissues. This may find use in the detection of toxic effects due to occupational exposures, or in the identification of workers who might be particularly sensitive to chemicals acting on the cholinergic system.

### Objectives

This project tests the hypothesis that muscarinic receptors on circulating lymphocytes could represent a marker of the same receptors in the CNS, the

lung, and other solid tissues; and that alterations of muscarinic receptors in such tissues due to environmental or genetic factors, to pharmacological treatment or to chemical exposure, will be detected by measuring receptor density, affinity, and function in lymphocytes.

### Methodology

Studies on muscarinic receptors on lymphocytes were conducted using <sup>3</sup>H-quinuclidinyl benzilate (<sup>3</sup>H-QNB) using a mixed population of lymphocytes isolated from rat spleen. The spleen was chosen for the initial characterization since a larger amount of cells can be obtained from one animal (as compared to isolating lymphocytes from blood). In further experiments, lymphocytes isolated from rat and human blood have also been utilized. Modulation of brain and lymphocyte muscarinic receptors has been studied *in vitro* and *in vivo* in rats treated with cholinergic drugs (oxotremorine, atropine) or an organophosphate insecticide (disulfoton).

### Significant Findings

An extensive series of experiments were performed to characterize the pharmacological specificity of the binding site for <sup>3</sup>H-QNB, and a large number of cholinergic and noncholinergic drugs were tested for their ability to inhibit specific binding of <sup>3</sup>H-QNB. These studies indicated that the muscarinic cholinergic binding site on lymphocytes had the same pharmacological characteristics as that in brain tissues, with, however, a much lower affinity for muscarinic antagonists. Experiments with circulating lymphocytes from rats and humans confirmed the results obtained with lymphocytes isolated from the spleen.

We also showed that prolonged exposures to cholinergic compounds *in vitro* and *in vivo* modulate muscarinic receptor binding in lymphocytes as well as in brain tissue. Exposure of rat splenic lymphocytes *in vitro* to oxotremorine caused a time- and concentration-dependent decrease in the density of <sup>3</sup>H-QNB binding sites. This decrease occurred only when incubation with oxotremorine was carried out at 37°C and not at 0-4°C, suggesting that it was not an artifact due to residual, unwashed, oxotremorine. The effect of oxotremorine was mimicked by two other cholinergic agonists, acetylcholine, and carbachol, and was antagonized by atropine, which when present alone, caused an increase in <sup>3</sup>H-QNB binding. *In vivo* exposures to oxotremorine or atropine (both at 20 mg/kg/day for 14 days via an ALZA minipump) caused a significant decrease (20-30%) and increase

(13-30%), respectively, of  $^3\text{H}$ -QNB binding in various brain areas as well as circulating lymphocytes. Repeated administrations of the organophosphorus insecticide disulfoton (2 mg/kg/day for 14 days, ip) caused significant reductions (59%-88%) of acetylcholinesterase activity in brain, lymphocytes, plasma, and red blood cells, as well as a 23-39% decrease of  $^3\text{H}$ -QNB binding in brain areas and circulating lymphocytes. These results indicate that muscarinic receptor on lymphocytes and in brain can be modulated by cholinergic drugs in a similar manner, suggesting that lymphocytes might be used as markers for cholinergic muscarinic receptors in nerve tissue.

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## Highway Maintenance Cohort Mortality Study

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Program Area: *Other Occupational Needs*  
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#### Importance to Occupational Safety and Health

The Minnesota Department of Health (MDH) reported an excess of leukemia among highway workers in Wheaton, Minnesota in 1979-1980 and concluded that a large-scale study of all highway maintenance workers was necessary. Highway maintenance work may involve exposure to a variety of potentially harmful materials, and workers may be at risk of leukemia or other important diseases. The number of past and current highway maintenance workers in the U.S. probably exceeds 500,000. Because of these concerns, a retrospective cohort mortality study of highway maintenance workers has been conducted.

#### Objectives

The first part of the highway maintenance worker studies was to compute standardized mortality ratios in order to evaluate which causes of death, if any, were elevated. This was completed in April 1987. Based on the results of the cohort mortality study, case-control studies were conducted for those causes of mortality that were elevated that had possible job-related increases (leukemia and injuries). Because injury mortality is only a small portion of injury morbidity, an injury surveillance system has been developed in order to monitor the environmental and ergonomic factors surrounding injuries. Finally, environmental studies are being conducted in order to evaluate exposures within the workplace. These environmental studies have been coupled with a cytogenetics case-control study.

## Methodology

A retrospective cohort mortality study of highway maintenance worker mortality was initiated in April 1985. Through various record sources, all men who ever worked in highway maintenance for the Minnesota Department of Transportation (MNDOT) between 1945 and 1984 were identified. Standardized mortality ratios (SMRs) were computed using computer programs developed by the MDH for this purpose. The indirect method of standardization was used. The comparison population was other Minnesotans of the same age, sex, and race.

Based on the results of the cohort mortality study, nested case-control studies were conducted for injuries and leukemia. Controls were selected from the cohort without replacement. For injuries, controls had to have been working at the Minnesota Department of Transportation (MNDOT) at the time the case was killed. For leukemia, the case and control had to have started work within a period of plus/minus 2 years. All relevant job history data were summarized and abstracted. Analysis was conducted using the Mantel-Haensel procedure.

An injury surveillance system was developed in order to assess every new injury regardless of severity. Reports of injury are submitted by employee supervisors to a central office where they are coded. Codes have been developed for environmental factors, injury severity, and equipment failures. In addition, traditional injury coding schemes have been modified. Injuries were classified based on care provider reports using ICD-9.

## Significant Findings

A total of 4,849 workers were included in the cohort study based on the 3 major eligibility criteria: (1) male; (2) worked at least one year as an HMW; and (3) employed by the MNDOT anytime between 1945 and 1984. The total number of deaths from all causes was 1,530, while 1,676 deaths were expected (SMR = 91;  $p < .01$ ). There was no trend with increasing duration of employment. The 9 percent deficit was accounted for by lowered mortality among all three major causes of death: heart disease, cancer, and cerebrovascular disease.

There were 278 cancer deaths overall, which was 17 percent fewer than expected (SMR = 83;  $p < .01$ ). There was no evidence of increasing risk with increasing duration of employment. The deficit in overall cancer deaths was affected by the observed deficits in several of the most common

types of cancer, including lung cancers and gastrointestinal cancers.

No overall elevation in mortality was noted for the category that included leukemias, Hodgkin's disease, lymphomas, and multiple myelomas (SMR = 95). Within this category, however, a slightly greater than expected number of leukemia deaths was found (SMR = 107). All of the 17 observed leukemia deaths occurred during the period 1965-1984. None were observed during the 1945-1964 time period, although 5 were expected. A statistically significant elevation in leukemia (SMR = 425;  $p < .01$ ) occurred among workers with 30-39 years of work experience and who started work between 1900 and 1944. Excess leukemia risk was found for both urban and rural workers. Overall, there were 19 cancers of the urinary system (SMR = 92), and there was no trend with increasing duration of employment or year started. There was a greater than expected number of deaths for those who died 40 to 49 years after the start of employment (SMR = 292;  $p < .05$ ).

Based on 17 deaths, the SMR for diseases of the genitourinary system was 77. Based on 8 deaths, there was no overall increase in deaths from chronic renal failure (SMR = 110). Risk did not increase with increasing duration of employment. There were 3 deaths, however, that occurred among men who had started work at least 50 years before their deaths, a number significantly greater than expected (SMR = 676;  $p < .05$ ).

Ninety-seven deaths were due to accidental causes (SMR = 121). Since transportation accidents were considered to be a category of special interest prior to the study, these findings were evaluated in greater detail. Transportation accidents involved any accidental death involving a motorized method of conveyance (car, truck, motorcycle, boat, snowmobile, etc.). Overall, there were 53 such accidental deaths (SMR = 138;  $p < .05$ ). Among urban workers, however, there was a statistically significant twofold excess compared to other Minnesotans. The greatest degree of excess occurred in 1975-1985 (SMR = 422;  $p < .05$ ).

At greatest risk were workers who had been employed less than five years. Although present data do not permit a complete assessment, it was found that 14 out of 53 transportation deaths occurred at the workplace. There were 44 deaths from all other types of accidents, which was not greater than expected. Ten of these are known to have occurred on the job.

Case-control studies have been completed for leukemia and injuries. Available job history information was insufficient to support a substantive case-control study for leukemia. For injuries, the

case-control study found no relationship between employee age, duration of employment, work in a rural or urban setting, or date of first employment and dying from a work-related injury.

#### Publications

Parker DL, Bender AP, Johnson RA, Anderson WK, Williams AN, Marbury MC, Mandel JS: The Minnesota Highway Maintenance Worker Cohort Mortality Study-Part I: Methods and Noncancer Mortality. *Am J Ind Med* 15:531-543, 1989

Bender Ap, Parker DL, Johnson RA, Anderson WK, Williams AN, Marbury MC, Mandel JS: The Minnesota Highway Maintenance Worker Cohort Mortality Study-Part II: Cancer Mortality. *Am J Ind Med* 15:545-556, 1989

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### Minimizing Dermal Exposure to Pesticides in Greenhouses

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Program Area: *Other Occupational Needs*  
Grant Number: *5 K01 OH00063-03*  
Start & End Dates: *05/01/87 - 04/30/90*  
Funding Level: *\$32,230 (\$96,655 Cum)*

#### Importance to Occupational Safety and Health

Greenhouse applicators are likely to receive substantial dermal exposures 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 critically affect exposure patterns.

#### Objectives

1. Identify the major variables influencing exposure during pesticide applications in greenhouses.

2. Evaluate the performance of protective clothing under normal application conditions.
3. Determine the effect of ventilation on dermal exposure during applications.
4. Determine the ability of a visual scoring system of fluorescent tracer deposition patterns to accurately categorize worker exposure.
5. Determine the ability of fluorescent tracer evaluation to serve as an educational tool in reducing dermal exposures.

#### Methodology

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

#### Significant Findings

The most significant findings to date are as follows:

1. Clothing normally designated as "chemical-resistant" can experience substantial breakthrough within a one-hour application period if the worker wets the clothing by direct contact with treated foliage.
2. Even rainsuit material (PVC) can be penetrated under such exposure conditions within one hour.
3. Ventilation systems which produce directed air movement can virtually eliminate aerosol deposition on skin surfaces of well-trained workers, but can substantially increase deposition among workers unfamiliar with such systems.
4. The ability to see exposure patterns through fluorescent tracer visualization had a demonstrable impact on the behavior of both workers and greenhouse managers.

## Hepatic Steatosis and Solvent: A Case-Control Study

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Program Area: *Other Occupational Needs*  
 Grant Number: 5 K01 OH00071-02  
 Start & End Dates: 09/29/87 – 09/28/90  
 Funding Level: \$26,852 (\$56,427 Cum)

### Importance to Occupational Safety and Health

Liver disease is the tenth leading cause of death and the ninth leading cause of years of potential life lost before the age of 65. Although documented and potential hepatotoxins are frequently used in the U.S., outbreaks of occupational liver disease occur only infrequently. Overt occupational liver disease is recognized and described only rarely. Other well-documented cases, such as infections and alcohol, are usually implicated even if their presence cannot be documented in specific cases. Other risk factors have been postulated, including obesity and diabetes, although the causal relationships are as yet unclear. Physicians are generally unaware of the various risk factors and unaware of implications of work exposures and of appropriate diagnostic or therapeutic consequences.

### Objectives

1. To estimate the risk for liver disease resulting from the interaction of alcohol, obesity, and solvents.
2. To develop educational materials for practicing physicians to alert them to occupational contributions to liver disease.

### Methodology

#### Case-control study of fatty liver disease (FLD)

Population: all cases of FLD disease referred to seven gastroenterology groups in Allegheny County over a two year period with biopsy-proven FLD were eligible (N=22). As controls, two 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, and average. Solvent exposure was quantified with ordinal scales of frequency, intensity, and duration. Specific exposures to pesticides, drycleaning fluids, paint strippers, and spot removers were also identified.

The study was terminated prematurely because individuals with FLD by sonogram or CT scanning techniques were no longer being biopsied unless they had occupational exposures, as biopsy habits in the gastroenterology community have changed. After two gastroenterologists made their biopsy decision dependent on the presence of occupational exposures, those patients were excluded, and the study was discontinued because of the threat of ascertainment bias.

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

#### 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 independent of diagnosis. Two control series are being used, both matched on age (within five years) and gender. A first series was selected from university GI clinics or one private gastroenterologist with a similar demographic profile of patients. A second series is being 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, 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 for analysis.

An educational case in trainer/student format has been developed. A version is being prepared for self-study.

### Significant Findings

No results from either case-control study are available as yet. Work has suggested that obesity is not a strong predictor of liver injury, although minor elevations in liver injury tests occur in up to 5% of the population. In addition, the question of human hepatotoxicity of 1,1,1-trichloroethane has been raised.

### Publications

Hodgson MJ, Heyl A, Van Thiel DH: Liver Disease Associated with Exposure to 1,1,1-Trichlorethane. *Archives of Internal Medicine* 149:1793-1798, 1989

Hodgson MJ, Van Thiel DH, Lauschus K, Karpf M: Liver Disease in Hazardous Waste Workers: The Role of Obesity. *Journal of Occupational Medicine* 31:238-242, 1989

Hodgson MJ, Goodman-Klein B, Van Thiel DH: Evaluating the Liver. In: *Medical Surveillance in Hazardous Waste Workers*, (ed. M Gochfeld), State-of-the-Art Reviews in Occupational Medicine, in press, 1989

Hodgson MJ, Van Thiel DH: Gastrointestinal Disease. *Control of Occupational Disease in Man*, (eds. B Levy, G Wagner, E Baker), APHA Monograph, in press, 1989

Hodgson MJ: Occupational Liver Disease—A Case Work-up. *Cases Studies in Occupational Disease*, (ed. R Sokas), in press, 1989

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### Ethical Decision-Making in Occupational Settings

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Program Area: *Other Occupational Needs*  
Grant Number: *5 K01 OH00072-02*  
Start & End Dates: *04/01/88 – 03/31/91*  
Funding Level: *\$32,400 (\$64,792 Cum)*

### Importance to Occupational Safety and Health

It is well known that workers are exposed to a variety of occupational hazards (e.g. biological, chemical, 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 based on employee health, screening without informed consent, invasion of privacy, lack of confidentiality, whistleblowing, use of incentives

to entice the worker to accept risk, and lack of providing adequate protective equipment are but a few problems that create ethical issues for health care professionals. This study has identified several ethical dilemmas that occupational health nurses (OHNs) find themselves grappling with but without satisfactory resolution. Decisions regarding these problems have far reaching consequences for health and well-being of the American workforce. Recognition of ethical problems and development of appropriate actions within an ethical framework will help guide policy development at all levels. In addition, discussion of these issues and approaches should be encouraged within occupational health curricula.

### Objectives

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

### Methodology

Three phases of research are proposed: Phase I, the descriptive study, is designed to develop and provide an inventory of recurrent ethical dilemmas experienced by a representative sample of practicing occupational health nurses through use of a four-round Delphi technique. Dilemmas will be categorized by a nurse ethicist to delineate the recurrent dilemmas. Through each round, dilemmas will be rated by the occupational health nurses as to the importance and impact of the dilemma (this phase is completed).

In Phase II, at least twelve practicing occupational health nurses representing geographic regions of the country will, through a workshop design, develop nursing actions responsive to each ethical dilemma (completed). These actions will be evaluated, by nurse ethicists, as to their relative congruence with the Code of Ethics. An instrument which will contain the ethical dilemmas and nursing actions will be pilot tested on 30 OHNs representative of large and small industries and hospitals for internal consistency, stability, validity,

and clarity. Subjects will be asked to specify actions as being both realistic and ideal (in progress).

In Phase III, the instrument will be administered nationally to 200 practicing OHNs to measure their responses to ethical dilemmas. Reliability and validity measures will be assessed. Descriptive analyses of nursing actions across dilemmas will be provided. Responses will be analyzed on variables identified in (3) above and 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 occupational health nurses, has been completed through use of a four-round Delphi technique procedure. By use of this technique, a consensus on concerns of most importance to a wide range of expert panel members was reached. In this phase, nearly 400 descriptions were received from 137 respondents. Ethical dilemmas described by the respondents were sent to Dr. Mila Aroskar, nurse ethicist, for categorization by dilemma type. Categories of ethical dilemmas were developed from the incidents themselves, from the general bioethics literature, other surveys of ethical problems/dilemmas in nursing, and the Code for Nurses. The concept of an ethical dilemma used to make determinations about the category was that the situation described (1) presented the OHN with a conflict of ethical/moral values, and/or (2) presented the OHN with a situation in which the nurse's moral (as contrasted with administrative or legal) obligations/responsibilities were not clear, and/or (3) the situation required some degree of ethical analysis as a primary consideration in order to reach resolution, i.e., decision and action.

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 obtained 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 re-averaged and dilemmas with combined average scores (for importance to the profession and impact on worker health) of at least 6.00 (on a 7.00 scale) were determined to be the most pressing problems. This resulted in a total of 20 ethical problems to be used in the Phase II Ethics Workshop held in Chapel Hill, North Carolina on November 9-11, 1989.

Nineteen individuals participated in the workshop to discuss and develop alternative strategies to address the dilemmas. Final strategies were developed for each dilemma discussed. These strategies are now being formally prepared to be reviewed by nurse ethicists as to their consistency with the Code of Ethics (per Methods). They will then be incorporated into the ethical decision-making instrument for pilot testing in early 1990 and final instrumentation for Phase III.

### Publications

Rogers B: Analysis of Ethical Problems: Exposures in the Workplace. Dangerous Properties of Industrial Materials Report, accepted for publication, 1990

Rogers B: Biological Hazards in Critical Care Nursing, Monograph, Health Sciences Media. 1989

Rogers B: Occupational Health Nursing Research. Recent Advances in Nursing, 1989

Rogers B: Employment Characteristics of Nurse Practitioners. The Nurse Practitioner 14:56-63, 1989

Rogers B: Florence Nightingale and Research - The Historical Link. AAOHN Journal 37:238-239, 1989

Rogers B: Ethical Dilemmas in Occupational Health. Occupational and Environmental Medicine Report 2:85-88, 1988

Rogers B: HIV Infection/AIDS in the Workplace. American Association of Occupational Health Nurses, 1988

Rogers B: Perspectives on Occupational Health Nursing. AAOHN Journal 36:151-155, 1988

Rogers B: Ethical Dilemmas in Occupational Health Nursing. AAOHN Journal 36:100-105, 1988

Rogers B, Sweeting S, Davis B: Selected Work Characteristics of Nurse Practitioners. Tarheel Nurse, 50: 13-14, 1988

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## Safety, Industrial Relations, and Productivity

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Program Area: *Other Occupational Needs*  
Grant Number: *5 K01 OH00075-02*  
Start & End Dates: *09/30/88 – 09/29/91*  
Funding Level: *\$32,400 (\$64,800 Cum)*

### Importance to Occupational Safety and Health

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

### Objectives

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

existing literature using a broad range of statistical data sources covering the 1980s.

### Methodology

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

### Significant Findings

The 1984 AFL-CIO survey contains information on worker perceptions of workplace hazards plus industry and occupation codes by means of which objective injury risks can be matched to the survey using data from the Bureau of Labor Statistics. Measures of worker responses include (1) reported dissatisfaction with the job; (2) intention to quit; and (3) willingness to vote in favor of union representation, should an NLRB election be held. Workers exposed to injury risks are less satisfied with their jobs, more likely to quit, and more willing to vote pro-union than are workers not exposed to hazards. These results hold strong after controlling for worker demographic variables (race, sex, education, age, etc.) and other job characteristic variables in addition to hazard (wages, fringe benefits, promotion possibilities, etc.). Compared to safe jobs, jobs presenting health and safety hazards are likely to offer low wages, few fringe benefits, poor promotion possibilities, and less job security; they are disproportionately staffed with minority workers.

Complete data on all closed union representation elections for the 1977-87 period were obtained from the National Labor Relations Board. To reduce the quantity of data to be analyzed, focus is on the 1977, 1980, 1983, and 1987 elections (approximately 15,000). The NLRB data are being used to answer two related but distinct questions concerning the influence of hazardous working conditions on the incidence and outcomes, respectively, of union representation elections. Results to date indicate that (1) representation

elections are much more frequent in hazardous industries than in safe industries, regardless of the year examined, and (2) the probability of union victory is higher in hazardous than in safe industries, though the effect is not large and varies across years. Given the much more frequent incidence of representation elections in hazardous than in safe industries, documented in (1), this implies that unions, through the election mechanism, are gaining substantially more members in hazardous than in safe industries.

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### Microsensor Array for the Identification of Organic Vapors

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Program Area: *Other Occupational Needs*  
Grant Number: *1 K01 OH00077-01*  
Start & End Dates: *07/15/89 – 07/14/92*  
Funding Level: *\$31,557 (\$31,557 Cum)*

#### Importance to Occupational Safety and Health

This work is motivated by the need for improved sensor technology in personal direct-reading monitoring equipment for organic vapors. Currently available instruments generally lack the selectivity necessary 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 comprised of 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 are being tested for their responses to several members of each of 13 classes of organic vapors. The sensor responses are 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 consist of monomeric, oligomeric, and polymeric compounds capable of rapidly and reversibly adsorbing organic vapors. Transient and steady-state responses from adsorption of the vapors will be utilized to achieve response selectivity. Simultaneous exposure of the sensor to industrially relevant vapor mixtures will be performed to verify the results predicted from the pattern recognition analysis.

#### Significant Findings

None to report at this time.

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### Mechanisms of Cytoskeletal Injury by Heavy Metals

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Program Area: *Other Occupational Needs*  
Grant Number: *5 R03 OH02321-02*  
Start & End Dates: *09/29/86 – 11/30/88*  
Funding Level: *\$20,068 (\$50,905 Cum)*

### Importance to Occupational Safety and Health

The results of this project indicate that microtubules vary in their sensitivity to the toxic metals  $\text{Cd}^{+2}$ ,  $\text{Hg}^{+2}$ ,  $\text{As}^{+3}$ , and  $\text{CH}_3\text{Hg}^+$ . In addition, the results demonstrate that  $\text{Cd}^{+2}$  can bind to and activate calmodulin, resulting in microtubule disassembly and inhibition of microtubule assembly *in vitro*. The results demonstrating  $\text{Cd}^{+2}$ -dependent binding of calmodulin to tubulin and MAPs in Western blots suggest that the enhanced inhibition of microtubule polymerization by  $\text{Cd}^{+2}$  in the presence of calmodulin is due to the  $\text{Cd}^{+2}$ -dependent binding of calmodulin to tubulin and MAPs. These findings raise the possibility that metal-induced microtubule damage may be involved in the expression of metal toxicity. More specifically, the finding that  $\text{Cd}^{+2}$  can substitute for  $\text{Ca}^{+2}$  in activating calmodulin, resulting in disturbances to microtubule dynamics, suggests that microtubule damage caused by the inappropriate activation of calmodulin by  $\text{Cd}^{+2}$  may be involved in  $\text{Cd}^{+2}$  toxicity. These results contribute to our understanding of the mechanisms of toxicity resulting from occupational exposure to heavy metals.

### Objectives

The overall aim of the project is to investigate the possible mechanisms by which metal induced microtubule damage occurs in cultured 3T3 cells exposed to  $\text{Cd}^{+2}$ ,  $\text{Hg}^{+2}$ , or  $\text{As}^{+3}$ . Because activated calmodulin is involved in regulating microtubule dynamics, the major hypothesis of the project is that  $\text{Cd}^{+2}$  and  $\text{Hg}^{+2}$  may affect microtubules by binding to and activating calmodulin. Because the ionic radii of  $\text{Cd}^{+2}$  (0.097nm) and  $\text{Hg}^{+2}$  (0.110nm) are so close to that of  $\text{Ca}^{+2}$  (0.099nm), both ions are capable of substituting for  $\text{Ca}^{+2}$  in calmodulin. In contrast,  $\text{As}^{+3}$  (0.053nm) is expected to affect microtubules via an interaction with tubulin sulphydryls.

### Methodology

The effects of metals on microtubule reassembly and on the microtubule networks in cultured cells and in detergent extracted cytoskeletons were monitored by indirect immunofluorescence microscopy and photography.

For the experiments involving *in vitro* microtubule assembly, bovine brain microtubule protein was purified according to the temperature-dependent disassembly-assembly method. Assembly of microtubules *in vitro* was done at 27°C and monitored spectrophotometrically

by measuring the increase in turbidity at 350nm following the addition of GTP to the reaction mixture. Permanent records of each experiment are provided by chart recordings of each turbidity scan.

The composition of bovine brain microtubule protein used for the *in vitro* assembly experiments (twice-cycled MT protein) was determined by discontinuous sodium dodecyl sulphate-polyacrylamide (7.5%) gel electrophoresis (SDS-PAGE), and staining with 0.25% Coomassie brilliant blue.

The twice-cycled microtubule protein was electroblotted onto nitrocellulose sheets, and overlaid with a biotinylated calmodulin probe in the presence of  $\text{Ca}^{+2}$  or  $\text{Cd}^{+2}$  to detect the presence of calmodulin-binding proteins.

### Significant Findings

Using the extracted cytoskeleton, we previously demonstrated that  $\text{Cd}^{+2}$ -induced microtubule disassembly can be prevented by the calmodulin inhibitors trifluoperazine or Compound 48/80. More recently, experiments were completed in which mixtures of  $\text{Ca}^{+2}$  or  $\text{Cd}^{+2}$ , at concentrations which by themselves do not affect microtubule networks, cause disassembly of microtubules in the extracted cytoskeleton. In addition, this  $\text{Ca}^{+2}$ / $\text{Cd}^{+2}$ -induced microtubule disassembly can be prevented by Compound 48/80, further supporting the earlier conclusion that  $\text{Cd}^{+2}$  affects microtubules by activating calmodulin in a manner similar to  $\text{Ca}^{+2}$ . We also found that  $\text{Hg}^{+2}$  and  $\text{CH}_3\text{Hg}^+$  are more potent inducers of microtubule disassembly in the extracted cytoskeleton than  $\text{Cd}^{+2}$ , and that calmodulin inhibitors had no effect on  $\text{CH}_3\text{Hg}^+$ -induced microtubule disassembly. However, inconsistent results with calmodulin inhibitors and  $\text{Hg}^{+2}$  were obtained.

The effects of metals on the kinetics for microtubule reassembly in 3T3 cells following removal of the microtubule-disrupting drug colcemid were determined. Microtubule reassembly is inhibited by micromolar concentrations of  $\text{Cd}^{+2}$ ,  $\text{Hg}^{+2}$ ,  $\text{As}^{+3}$ , and  $\text{CH}_3\text{Hg}^+$ . This inhibition was originally planned to be monitored by measuring the lengths of fixed and immunofluorescently stained microtubules in photographs. However, ELISA protocols for more accurate quantitation of polymerized tubulin are being developed and standardized in this lab.

In order to more directly determine that  $\text{Cd}^{+2}$  can affect microtubules by binding to and activating calmodulin, we investigated the inhibitory effect of  $\text{Cd}^{+2}$  on the assembly of purified brain microtubule protein *in vitro* in the absence and presence of calmodulin. Micromolar concentrations of  $\text{Cd}^{+2}$

alone inhibited microtubule assembly. The addition of calmodulin enhanced the inhibitory effect of calmodulin, further reducing the rate. Furthermore, this enhanced inhibition is reversible by Compound 48\80. Calmodulin alone has no effect. The enhanced inhibition of microtubule assembly in the presence of  $Cd^{+2}$  and calmodulin, and its reversal by Compound 48\80, indicates that  $Cd^{+2}$  is binding to and activating calmodulin.

SDS-PAGE of microtubule protein used in the *in vitro* assembly experiments and Coomassie blue staining of gels reveals the presence of tubulin and microtubule-associated proteins (MAPs) in these preparations. Calmodulin has been shown to bind to tubulin and MAPs in the presence of  $Ca^{+2}$ , and inhibit microtubule assembly, suggesting a possible mechanism for the  $Cd^{+2}$ \calmodulin-dependent enhancement of inhibition.

To directly test whether  $Cd^{+2}$  could support the binding of calmodulin to tubulin and MAPs, biotinylated-calmodulin was used as a probe in conjunction with avidin-horseradish-peroxidase and chloronaphthol to identify calmodulin-binding proteins in Western blots of twice-cycled microtubule protein. MAP 2, tubulin, and tau region proteins were labelled by biotinylated-calmodulin in the presence of  $Ca^{+2}$  or  $Cd^{+2}$ . This labelling was abolished by EGTA. These results show that  $Cd^{+2}$  can support the binding of calmodulin to known calmodulin-binding proteins in twice-cycled microtubule protein.

#### Publications

Perrino BA, Chou IN: Calmodulin Modulation of Adverse Effects of  $CD^{+2}$  on Microtubules and Tubulin Polymerization *In Vitro*. *Toxicology In Vitro*, in press, 1989

Perrino BA, Chou IN: Cytoskeletal Injury Resulting from the Interaction of Calmodulin with Metal Compounds. Proc Sixth International Conference of Heavy Metals in the Environment, Vol 1: 332-336, 1987. This paper was presented as the Keynote Address of the Session on Health Effects: Cadmium and Mercury, Sept. 16, 1987

Perrino BA, Chou IN: Inhibition of Microtubule Reassembly by Cadmium, Arsenite, and Methylmercury in Cultured Fibroblasts. *Toxicologist* 7:71, 1987 (Abstract)

## Disease Prevention Through Workers' Compensation

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Program Area: *Other Occupational Needs*  
Grant Number: 1 R03 OH02550-01  
Start & End Dates: 09/30/88 - 09/29/89  
Funding Level: \$23,426 (\$23,426 Cum)

### Importance to Occupational Safety and Health

One of the basic objectives of the workers' compensation program is the prevention of work-related injuries and diseases. Most employees work for employers who are experience-rated (insurance costs vary with benefits paid). Preventive activities thus can result in lower costs to employers.

### Objectives

In order for experience-rating to provide the proper economic incentive to employers to undertake preventive activities, the workers' compensation program must pay benefits to workers whose disabilities are caused by the workplace. Previous studies have concluded that many occupational diseases are not compensated by workers' compensation, thus undermining the basic preventive objective.

The basic objective of the project was to examine the handling of occupational disease claims by the New York workers' compensation program in order to determine if there were features of the program that could be modified in order to facilitate the processing of disease claims. Disease claims were compared with injury claims to determine if there were differences in outcomes such as delays and propensity to litigate. The outcomes for six types of diseases were also compared.

### Methodology

The methodology consisted of two basic approaches. First, a data base of workers' compensation cases closed between 1964 and 1983 was analyzed. Quantitative estimates were made of the changes over time in the magnitude of the occupational disease problem in New York. Six

types of occupational diseases and two types of injuries were compared using various statistical tests (e.g., ANOVA and multiples regressions). The comparisons involved several case output measures (e.g., delays in deciding the cases) and various explanatory variables measuring personal characteristics (e.g., age and type of injury or disease) and policy variables (e.g., did the statute provide a presumption of compensability for the particular disease).

The second phase of the study consisted of a series of structured interviews with practitioners involved in the New York workers' compensation program, including physicians, lawyers, administrators, and administrative law judges. The purpose of the interviews was to help identify the features that facilitate or hinder the compensation of occupational disease claims.

### Significant Findings

Disease and injury cases have widely divergent outcomes in the New York workers' compensation program. Disease cases cost more, take longer to decide, are more likely to be litigated, and involve higher legal fees than injury cases. Among the six types of disease cases, the use of causation-scheduling reduced costs, delays, litigation, and legal fees. Causation-scheduling, which establishes a presumption that the disease is work-related, is used for some diseases (e.g., silicosis) but not for others (e.g., heart disease).

The disparity between the handling of injuries and diseases in terms of the delays and litigation suggests that the New York workers' compensation program is not providing appropriate coverage to occupational diseases. In turn, this means that the experience-rating in workers' compensation is providing insufficient stimulus to employers to prevent occupational diseases. If, however, modifications were made in criteria and procedures used to compensate occupational diseases, such as the greater use of causation-scheduling, then the workers' compensation program would more effectively meet its objective of preventing work-related injuries and diseases.

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## Biological Monitoring for Exposure to Complex Mixtures

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Program Area: *Other Occupational Needs*  
Grant Number: *5 R03 OH02555-02*  
Start & End Dates: *09/30/88 - 09/29/90*  
Funding Level: *\$22,091 (\$41,217 Cum)*

### Importance to Occupational Safety and Health

An important problem in occupational health is the assessment of exposure to chemical mixtures. This work is providing new tools to identify the sources of mixed chemical exposure and developing a new technique of biological monitoring for mixed chemical exposure.

### Objectives

This work involves an investigation of the patterns of chemicals in air samples and patterns of metabolites in urine samples of exposed workers. The short-term objective of this work is to develop methods for measuring exposure to complex mixtures. The work involves the analysis of air sample data and urine sample data using pattern recognition techniques. The results of pattern recognition analysis are being used in the identification and quantitation of exposure. The long-term objective of the work is the reduction of occupational and environmental disease by the improved identification and management of chemical exposure.

### Methodology

This work involves the use of conventional passive and active sampling techniques plus gas chromatography to measure solvents in air samples. In addition, a published method using hydrolysis and gas chromatography is used to measure solvent metabolites in urine. The data obtained from the gas chromatography are analyzed by pattern recognition techniques to identify patterns of exposure (cluster analysis) and to classify exposures (classification analysis). Principal component analysis has been used in the initial data analysis.

Other techniques, such as log-linear analysis, will be used to confirm the findings of principal component analysis.

### Significant Findings

A group of workers in printing, bookbinding, and photocopy have been used as subjects for the study. Air samples were collected, using both passive and active samplers. Urine samples were concurrently collected from the same workers. Air samples were analyzed by gas chromatography/flame ionization detection (GC/FID). Urine samples have been analyzed for metabolites, also using GC/FID. An initial analysis of air sample data has shown that workers have characteristic patterns of exposure, which appear to be primarily determined by type of work and work practices.

be used to help establish a more accurate workplace exposure level of vanadium. In addition, the approaches used 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 whether the mechanism by which vanadium treatment interferes with the mouse resistance to *Listeria monocytogenes* is through the interference with peritoneal macrophage ingestion and/or processing of the pathogen, or through an 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 peritoneal macrophages as related to their phagocytic and bactericidal functions will also be explored.

### Methodology

Female B<sub>6</sub>C<sub>3</sub>F<sub>1</sub> mice weighing 18-20 g will be dosed IP every three days for 3 or 6 weeks with ammonium metavanadate (NH<sub>4</sub>VO<sub>3</sub>) solution in 0.1 M phosphate buffer (pH 7.2), NH<sub>4</sub>Cl solution, or phosphate buffer. The doses of NH<sub>4</sub>VO<sub>3</sub> will be 10.0, 5.0, or 2.5 mg/kg body weight. Three days after the final challenge, the mice will be treated with *Listeria monocytogenes* for clearance studies, or sacrificed for the collection of the peritoneal macrophages. 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 x 10<sup>3</sup> *Listeria*.

The intracellular killing of *Listeria* by peritoneal macrophages will also be performed. Peritoneal macrophages collected from *Listeria* challenged animals will be subjected to freeze-thawing treatment in test tubes at 0, 15, 30, or 60 min for the determination of intracellular bacterial numbers on trypticase soy agar.

To assay the activities of glucose-6-phosphate dehydrogenase, glutathione reductase and glutathione peroxidase, peritoneal macrophages at 10<sup>7</sup>/ml are subjected to freeze-thawing to prepare cytolysates for protein and enzyme assays. The release from peritoneal macrophages of  $\beta$ -galactosidase, lysozyme, hydrogen peroxide, leukotriene C, and interleukin-1 will be determined with the appropriate methods. In addition, the superoxide anion production and the reduced and oxidized glutathione content in peritoneal macrophages will also be assayed to determine the effect of vanadium treatment. The effects of vanadium treatment on macrophage cytoskeleton

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## Toxicological Effect of Vanadium on the Macrophage Response to *Listeria* Challenge

Cheng-i Wei, Ph.D.  
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Food Science and  
Human Nutrition Department  
Gainesville, Florida 32611-0163

Program Area: *Other Occupational Needs*  
Grant Number: 5 R03 OH02583-02  
Start & End Dates: 04/01/88 - 03/31/90  
Funding Level: \$21,750 (\$43,500 Cum)

### Importance to Occupational Safety and Health

Most information on human vanadium exposure is of occupational origin. 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 exposure will affect the host immunity and render the workers more susceptible to infectious agents. The information obtained in this study, using mice as a model, will contribute to the understanding of the underlying mechanisms involved in vanadium toxicity and its immunomodulating activity in the body. Most of the reported immunotoxicity studies are primarily based on analyses of macrophage viability and phagocytic activity. The information obtained can

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 will be employed to determine the significance of vanadium treatment of the parameters investigated. Analysis of variance (ANOVA), Duncan's comparison of means, and the Student's t-test will be used to determine significance as well as any dose- or time-dependent effects.

### Significant Findings

Vanadium treatment of mice resulted in altered patterns of *Listeria monocytogenes* clearance from the peritoneal cavity, liver, and spleen. Mice exposed to vanadate for 6 weeks showed a dose-dependent increase in *Listeria* in the spleen and liver, and also displayed higher levels at time points earlier than in control mice. The total *in vitro* phagocytic uptake of *Listeria* by peritoneal macrophages (PEM) was consistently decreased as a function of infection period. Similarly, intracellular killing of *Listeria* was decreased although the PEM from vanadate-treated and control mice were more bacteriostatic than bactericidal. Population distribution of *Listeria* within infected PEM were not affected by host pretreatment with vanadate. Thus, vanadate exposure interfered with both the uptake and ultimate intraphagolysosomal killing of *Listeria* by PEM. The results suggest that the alteration in host resistance is due, in part, to the effects of vanadate on some previously reported (Cohen and Wei, J Leuk Biol 44:122, 1988) PEM biochemical functions which would result in decreased phagocytosis and killing and ultimately in a rapid onset of host death.

### Publications

Cohen MD, Fukayama MY, Wei CI: Immunotoxicological Studies of Ammonium Metavanadate in Mice. In: Biological Monitoring of Exposure to Metals, John Wiley and Sons, Inc., in press, 1989

Iwusu-Yaw J, Cohen MD, Fernando SY, Wei CI: An Assessment of the Genotoxicity of Vanadium. Toxicology Letters, in press, 1989

Cohen MD, Chen CM, Wei CI: Decreased Resistance to *Listeria Monocytogenes* in Mice Following Vanadate Exposure: Effects Upon the Function of Macrophages. Int J Immunopharmacol 11:285-292, 1989

Wei CI, Cohen MD: Decreased Resistance to *Listeria Monocytogenes* in Mice Following Vanadium Exposure: Effects upon the Function of Macrophages. The Toxicologist 9:17, 1989 (Abstract)

Cohen MD, Wei CI: Effect of Ammonium Metavanadate Treatment upon Murine Peritoneal Macrophage Respiratory Burst-Related Biochemistry. FASEB J 2:A915, 1988

Cohen MD, Wei CI: Effects of Ammonium Metavanadate Treatment upon Macrophage Glutathione Redox Cycle Activity, Superoxide Production, and Intracellular Glutathione Status. J Leuko Biol 44:122-129, 1988

Sen AC, Cohen MD, Wei CI: Vanadium Inhibition of Glucose-6-phosphate Dehydrogenase and Glutathione Reductase *In Vitro*. FASEB J 2:A1819, 1988

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## Development of a Low-Cost Ethylene Oxide Detector

Cynthia L. Benner, Ph.D.

ADA Technologies, Inc.

304 Inverness Way South, Suite 110  
Englewood, Colorado 80112

Program Area: *Other Occupational Needs*

Grant Number: 1 R43 OH02662-01

Start & End Dates: 09/30/88 - 03/31/89

Funding Level: \$46,907 (\$46,907 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 in 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 instrument will use room air as the carrier gas. 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 I program was conducted during two periods: (1) the original six-month grant period between September 30, 1988 and March 31, 1989; and (2) a non-funded period in November and December 1989 in which supplemental experiments were performed. The purpose of the supplemental experiments was to address the criticisms of NIOSH Safety and Occupational Health Study Section reviewers who had critiqued the Phase II grant application. The results of these later experiments were incorporated in the revised Phase II application.

The methodology used in the original Phase I study was as follows. A chromatographic column was chosen in Task 1 based on its ability to effectively separate EtO from interfering species, and ability to elute EtO in one minute or less at room temperature. In Task 2, a solid state semiconductor sensor was chosen for the measurement of EtO, and preliminary testing of the sensor was performed. Methods to control ambient humidity were also investigated. Task 3 involved the design of the catalyst bed. The initial purpose of the catalyst bed was to remove EtO from the air stream while allowing all other compounds to pass. The EtO instrument flow system was assembled in Task 4, and both the water saturator and dryer were tested as a humidity control device. The results of the humidity tests showed that a reference sensor

was required in order to correct for changes in the sensor signal due to humidity. In Task 5, the instrument was calibrated by sampling 0.1 ppm to 31 ppm EtO in a Tedlar bag attached to the flow system pump. The heater voltage of the sensors was varied to determine the effect on the sensor response to EtO. Finally, the instrument was tested for response to two common interferences, dichlorodifluoromethane (0.7-50 ppm) and isopropyl alcohol (IPA) (49-380 ppm).

The experiments performed for the revised Phase II grant application focused on solving problems identified by the reviewers. The length of the chromatographic column was increased, and the column temperature was controlled at 65°C. The sensor block temperature was maintained at 30°C by wrapping the sensor block with thermal insulation material. The new EtO instrument design requires only one sensor instead of two matched sensors. The new catalyst bed removes all combustible compounds, providing clean air for carrier gas. Performance testing of the new instrument was carried out by filling a 45-liter Tedlar bag with the desired concentration of EtO and manually injecting 100-microliter samples from the bag.

### Significant Findings

An important result of the original Phase I investigation was that EtO was measurable in a room air background at the target detection limit of 0.1 ppm. Also, dichlorodifluoromethane did not interfere with the measurement of 0.1 ppm to 7 ppm EtO. Cylinder gases were not required for either the carrier gas or as support gases for the detector. The EtO retention time was 17 seconds, with an injection time of 5 seconds and total cycle time of 3 minutes. This instrument is capable of operating continuously in a stand-alone mode.

The most significant problem with the original EtO instrument was the effect of IPA on the EtO signal. Because of the non-specificity of the detector, it was necessary to improve the separation of EtO from interfering species. This was accomplished by increasing the column length from 1.5 feet to 10 feet in the re-submittal experiments. With the new column, 1 to 8 ppm EtO were easily separated from 1,000 ppm IPA and methanol. Water was also separated from EtO in the longer column, eliminating the need for the reference sensor. In the Phase II prototype EtO monitor, different methods to avoid exposure of the sensor to interferences and water will be explored. Temperature effects are not a concern with the new instrument design because the temperature of both the column and sensor block are controlled.

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**GRANTS ACTIVE DURING FY89**

	COMPETING GRANTS		TOTAL GRANTS	
	No. of Awards	Amount of Awards	No. of Awards	Amount of Awards
<b>Grants from FY89 Budget (\$6.196M)</b>				
Research Project Grants (R01)	18	\$2,074,370	44	\$5,244,715
Career Development Grants (K01)	3	\$115,848	9	\$307,578
Small Grants (R03)	10	\$212,079	16	\$339,630
Other Grants	1	\$46,820	3	\$303,897
Subtotal	32	\$2,449,117	72	\$6,195,820
<b>Grants from FY88 Budget (\$6.224M)</b>				
Research Project Grants (R01)	6	\$516,106	17	\$2,046,461
Career Development Grants (K01)	1	\$32,400	4	\$123,952
Small Grants (R03)	3	\$63,414	10	\$199,911
Other Grants	1	\$46,907	1	\$46,907
Subtotal	11	\$658,827	32	\$2,417,231
<b>Grants from FY87 Budget (\$6.501M)</b>				
Research Project Grants (R01)	1	\$28,147	6	\$632,886
Career Development Grants (K01)	0	\$0	0	\$0
Small Grants (R03)	1	\$21,887	2	\$47,656
Other Grants	0	\$0	0	\$0
Subtotal	2	\$50,034	8	\$680,542
<b>Awards from all Years</b>				
Research Project Grants	25	\$2,618,623	67	\$7,924,062
Career Development Grants	4	\$148,248	13	\$431,530
Small Grants	14	\$297,380	28	\$587,197
Other Grants	2	\$93,727	4	\$350,804
<b>TOTAL</b>	<b>45</b>	<b>\$3,157,978</b>	<b>112</b>	<b>\$9,293,593</b>

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**FY89 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	6	\$652,554	12	\$1,221,549	18%
Musculoskeletal Injuries	3	\$81,098	6	\$459,789	7%
Occupational Cancers	4	\$160,722	6	\$339,478	5%
Traumatic Injuries	2	\$42,066	4	\$219,314	4%
Cardiovascular Diseases	1	\$26,630	1	\$26,630	0%
Reproductive Disorders	0	\$0	3	\$201,721	3%
Neurotoxic Disorders	2	\$377,292	4	\$557,834	10%
Noise-Induced Hearing Loss	1	\$18,246	3	\$266,894	4%
Dermatologic Disorders	2	\$235,745	3	\$384,826	6%
Psychologic Disorders	0	\$0	1	\$82,839	1%
Control Techniques	4	\$169,994	7	\$347,069	6%
Respirator Research	1	\$46,820	7	\$725,808	12%
Other Occupational Needs	6	\$637,950	15	\$1,362,069	24%
<b>TOTAL</b>	<b>32</b>	<b>\$2,449,117</b>	<b>72</b>	<b>\$6,195,820</b>	<b>100%</b>

**FY89 GRANT AWARDS BY REGION AND STATE**  
**72 GRANTS TOTTALLING \$6,195,820, AMOUNTS IN \$1,000's**



	<u>No.</u>	<u>Amt.</u>	<u>(Per.)</u>		<u>No.</u>	<u>Amt.</u>	<u>(Per.)</u>
Region I	4	\$285,151	( 4.6%)	Region II	8	\$843,638	(13.6%)
Connecticut	2	\$233,156	( 3.8%)	New Jersey	2	\$51,455	( 0.8%)
Massachusetts	2	\$51,995	( 0.8%)	New York	6	\$792,183	(12.8%)
Region III	8	\$595,169	( 9.6%)	Region IV	10	\$624,035	(10.1%)
Maryland	4	\$285,426	( 4.6%)	Alabama	1	\$18,859	( 0.3%)
Pennsylvania	2	\$118,030	( 1.9%)	Florida	3	\$139,132	( 2.2%)
Virginia	2	\$191,713	( 3.1%)	Kentucky	1	\$21,825	( 0.4%)
Region V	22	\$1,800,520	(29.1%)	North Carolina	5	\$444,219	( 7.2%)
Illinois	4	\$362,275	( 5.8%)	Region VI	6	\$561,488	( 9.8%)
Indiana	1	\$59,219	( 1.0%)	Louisiana	2	\$139,696	( 2.2%)
Michigan	8	\$730,449	(11.8%)	Oklahoma	3	\$259,238	( 4.2%)
Ohio	9	\$648,577	(10.5%)	Texas	2	\$209,374	( 3.4%)
Region VII	1	\$150,104	( 2.4%)	Region VIII	1	\$158,023	( 2.6%)
Kansas	1	\$150,104	( 2.4%)	Colorado	1	\$158,023	( 2.6%)
Region IX	9	\$753,580	(12.1%)	Region X	2	\$377,292	( 6.1%)
Arizona	2	\$50,590	( 0.8%)	Washington	2	\$377,292	( 6.1%)
California	7	\$702,990	(11.3%)				

<u>Grant Number</u>	<u>Principal Investigator</u>	<u>Current Funding</u>	<u>Page</u>
<i>Research Project Grants (R01)</i>			
5 R01 OH00823-10	Mohamed B. Abou-Donia, Ph.D.	\$158,717	69
5 R01 OH00835-11	William J. Swartz, Ph.D.	\$47,743	59
5 R01 OH00978-09	James R. Trudell, Ph.D.	\$281,968	125
2 R01 OH01122-07A1	Charles W. Kauffman, Ph.D.	\$204,109	50
7 R01 OH01152-09	Donald Henderson, Ph.D.	\$174,548	76
5 R01 OH01301-06	Klaus Willeke, Ph.D.	\$159,322	112
5 R01 OH01595-05	William C. Hinds, Sc.D.	\$88,130	113
5 R01 OH01630-07	Edwin M. Uyeki, Ph.D.	\$150,104	128
5 R01 OH01632-02	Neil J. Zimmerman, Ph.D.	\$123,194	114
5 R01 OH01968-04	Rosalind C. Barnett, Ph.D.	\$212,952	92
5 R18 OH01981-02	Scott C. Clark, Ph.D.	\$165,593	130
5 R01 OH02003-03	Mohamed B. Abou-Donia, Ph.D.	\$198,511	70
5 R01 OH02005-06	Philip I. Harber, M.D.	\$76,720	115
5 R01 OH02067-05	G. Marie Swanson, Ph.D.	\$154,118	40
5 R01 OH02076-03	Dean E. Carter, Ph.D.	\$131,079	11
5 R01 OH02091-05	James J. Nordlund, M.D.	\$149,081	85
5 R01 OH02114-03	William W. Merrill, M.D.	\$135,956	12
5 R01 OH02128-05	William W. Clark, Ph.D.	\$151,063	77
2 R01 OH02132-04	Nurtan A. Esmen, Ph.D.	\$68,689	97
5 R01 OH02148-05	Stephen F. Cleary, Ph.D.	\$135,956	60
2 R01 OH02149-04A1	Ghulam A.S. Ansari, Ph.D.	\$130,517	131
5 R01 OH02154-02	John S. Evans, Sc.D.	\$49,254	117
1 R01 OH02162-01A1	Phyllis K. Mansfield, Ph.D.	\$118,781	93
5 R01 OH02214-03	William E. Brown, Ph.D.	\$100,008	13
5 R01 OH02221-02	Stephen M. Rappaport, Ph.D.	\$135,524	133
5 R01 OH02230-02	Bernard C. Jiang, Ph.D.	\$18,859	98
5 R01 OH02254-02	Walter F. Stewart, Ph.D.	\$163,127	51
1 R01 OH02260-01A2	Young H. Yoon, Ph.D.	\$97,397	118
5 R01 OH02264-05	Andrew Ghio, M.D.	\$153,757	15
1 R01 OH02277-01A2	David Warshawsky, Ph.D.	\$166,651	17
5 R01 OH02284-02	Eva R. Glazer, M.D.	\$5,275	41
5 R01 OH02288-02	Philip I. Harber, M.D.	\$141,724	134
1 R01 OH02298-01A2	Kenneth D. Rosenman, M.D.	\$95,886	18
5 R01 OH02303-02	Steven P. Levine, Ph.D.	\$95,360	136
5 R01 OH02317-05	Roger P. Hamernik, Ph.D.	\$192,891	79
5 R01 OH02329-03	Richard P. Garrison, Ph.D.	\$98,997	99
5 R01 OH02332-03	Edward H. Bergofsky, M.D.	\$142,347	18
5 R01 OH02352-02	Venkat Venkatasubramanian, Ph.D.	\$59,219	100
1 R01 OH02373-01A1	Walter F. Stewart, Ph.D.	\$169,560	62
1 R01 OH02391-01A2	Nabih R. Asal, Ph.D.	\$182,003	137
5 R01 OH02392-02	Michael R. Flynn, Sc.D.	\$55,961	102
5 R01 OH02404-02	Steven P. Levine, Ph.D.	\$114,857	138
5 R01 OH02417-03	Joseph T. Hjelle, Ph.D.	\$96,833	139
1 R01 OH02421-01A1	David C. Christiani, M.D.	\$78,510	20
5 R01 OH02434-02	Mohamed M. Ayoub, Ph.D.	\$78,857	32
1 R01 OH02437-01A1	David Leith, Sc.D.	\$77,670	102
5 R01 OH02540-02	John G. Casali, Ph.D.	\$55,757	81

<u>Grant Number</u>	<u>Principal Investigator</u>	<u>Current Funding</u>	<u>Page</u>
5 R01 OH02564-02	Arthur B. DuBois, M.D.	\$254,263	119
1 R01 OH02568-01	Waldemar Karwowski, Ph.D.	\$26,539	103
1 R01 OH02571-01	Irvin Schonfeld, Ph.D.	\$82,839	95
5 R01 OH02574-02	Susan P. Baker, M.P.H.	\$204,202	33
1 R01 OH02586-01	J. Paul Leigh, Ph.D.	\$28,147	140
5 R01 OH02591-02	Shihab Asfour, Ph.D.	\$95,632	34
1 R01 OH02593-01A1	E. Neil Schachter, M.D.	\$131,942	20
5 R01 OH02601-02	Carol J. Garrett, Ph.D.	\$158,023	52
1 R01 OH02611-01	Susan T. Bagley, Ph.D.	\$81,993	42
1 R01 OH02614-01A1	Henry H. Emurian, Ph.D.	\$26,782	58
1 R01 OH02618-01	Yehia Y. Hammad, D.Sc.	\$91,953	21
1 R01 OH02621-01	William S. Marras, Ph.D.	\$33,248	35
1 R01 OH02622-01	Regina M. Santella, Ph.D.	\$209,850	87
1 R01 OH02629-01	Harvey Checkoway, Ph.D.	\$152,175	72
1 R01 OH02647-01	George P. Hemstreet, III, M.D.	\$30,415	44
1 R01 OH02651-01	James K. Hardy, Ph.D.	\$49,809	142
1 R01 OH02663-01	Edward T. Zellers, Ph.D.	\$95,489	143
1 R01 OH02666-01	Steven P. Levine, Ph.D.	\$148,575	144
1 R01 OH02683-01	William Daniell, M.D.	\$230,717	73
1 R01 OH02726-01	David F. Goldsmith, Ph.D.	\$144,447	23

Career Development Grants (K01)

5 K01 OH00054-03	Lucio G. Costa, Ph.D.	\$32,300	145
5 K01 OH00055-03	David L. Parker, M.P.H.	\$32,400	146
7 K01 OH00060-01	Christopher G. Murlas, M.D.	\$32,400	23
5 K01 OH00063-03	Richard A. Fenske, Ph.D.	\$32,332	148
5 K01 OH00067-03	Linda M. Hanna, Ph.D.	\$29,956	25
5 K01 OH00068-03	Clifton D. Crutchfield, Ph.D.	\$32,344	120
5 K01 OH00071-02	Michael J. Hodgson, M.D.	\$26,852	149
5 K01 OH00072-02	Bonnie Rogers	\$32,400	150
5 K01 OH00073-02	David I. Bernstein, M.D.	\$32,400	27
5 K01 OH00075-02	James C. Robinson, Ph.D.	\$32,400	152
1 K01 OH00076-01	Paul W. Brandt-Rauf, Sc.D., M.D.	\$32,314	45
1 K01 OH00077-01	Edward T. Zellers, Ph.D.	\$31,557	153
1 K01 OH00078-01	Lorraine M. Conroy, Sc.D.	\$51,997	105

Small Grants (R03)

5 R03 OH02236-02	Dennis J. Murphy, Ph.D.	\$16,743	106
5 R03 OH02321-02	Brian A. Perrino	\$20,068	153
5 R03 OH02376-02	John D. Hamilton	\$21,003	63
5 R03 OH02380-02	John R. Wilkins, Ph.D.	\$21,358	64
5 R03 OH02383-02	Linda A. Shortridge	\$6,518	65
1 R03 OH02422-01	William E. Daniell, M.D.	\$21,887	107
5 R03 OH02425-02	Carol E. O'Neil, Ph.D.	\$22,500	28

<u>Grant Number</u>	<u>Principal Investigator</u>	<u>Current Funding</u>	<u>Page</u>
5 R03 OH02433-02	Mun-Fai Leung	\$26,700	88
5 R03 OH02548-02	David A. Savitz, Ph.D.	\$21,675	67
1 R03 OH02550-01	John F. Burton, Jr., Ph.D.	\$23,426	155
5 R03 OH02555-02	Robert C. Spear, Ph.D.	\$22,091	156
5 R03 OH02578-02	Michael T. Tseng, Ph.D.	\$21,825	74
5 R03 OH02579-02	Gary Sorock, Ph.D.	\$19,225	53
1 R03 OH02580-01	Riedar K. Oestestad	\$18,639	121
1 R03 OH02583-01	Cheng-i Wei, Ph.D.	\$21,750	157
1 R03 OH02627-01	Thomas G. Robins, M.D.	\$21,349	29
5 R03 OH02631-02	Anne M. Sweeney	\$18,022	67
5 R03 OH02632-02	Lorraine E. Twerdok	\$24,638	46
1 R03 OH02653-01	Richard J. Wickstrom	\$20,675	55
1 R03 OH02654-01	Carl M. Shy, M.D., Dr.P.H.	\$21,675	30
1 R03 OH02655-01	Ken C. Lin	\$25,895	90
1 R03 OH02657-01	Susan F. Velazquez	\$16,000	48
1 R03 OH02659-01	Richard S. Hopkins, M.D.	\$21,391	56
1 R03 OH02667-01	Edward T. Zellers, Ph.D.	\$23,834	109
1 R03 OH02671-01	Glen M. Miller, Ed.D.	\$18,246	83
1 R03 OH02680-01	Lorraine M. Conroy, Sc.D.	\$16,513	110
1 R03 OH02684-01	Donna L. Wheeler	\$21,750	36
1 R03 OH02689-01	Laura Punnett, Sc.D.	\$26,100	38

*Small Business Grants (R43, R44)*

1 R43 OH02662-01	Cynthia L. Benner, Ph.D.	\$46,907	158
1 R43 OH02698-01	Bruce L. Roberts	\$46,820	123
5 R44 OH02312-03	Joseph R. Stetter, Ph.D.	\$199,843	122

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Abou-Donia, Mohamed B., Ph.D.	Neurotoxic Disorders	5 R01 OH00823-10	69
Abou-Donia, Mohamed B., Ph.D.	Neurotoxic Disorders	5 R01 OH02003-03	70
Ansari, Ghulam A.S., Ph.D.	Other Occupational Needs	2 R01 OH02149-04A1	131
Asal, Nabih R., Ph.D.	Other Occupational Needs	1 R01 OH02391-01A2	137
Asfour, Shihab Ph.D.	Musculoskeletal Injuries	5 R01 OH02591-02	34
Ayoub, Mohamed M., Ph.D.	Musculoskeletal Injuries	5 R01 OH02434-02	32
Bagley, Susan T., Ph.D.	Occupational Cancers	1 R01 OH02611-01	42
Baker, Susan P., M.P.H.	Musculoskeletal Injuries	5 R01 OH02574-02	33
Barnett, Rosalind C., Ph.D.	Psychological Disorders	5 R01 OH01968-04	92
Bergofsky, Edward H., M.D.	Occupational Lung Diseases	5 R01 OH02332-03	18
Brown, William E., Ph.D.	Occupational Lung Diseases	5 R01 OH02214-03	13
Carter, Dean E., Ph.D.	Occupational Lung Diseases	5 R01 OH02076-03	11
Casali, John G., Ph.D.	Noise-Induced Hearing Loss	5 R01 OH02540-02	81
Checkoway, Harvey, Ph.D.	Neurotoxic Disorders	1 R01 OH02629-01	72
Christiani, David C., M.D.	Occupational Lung Diseases	1 R01 OH02421-01A1	20
Clark, Scott C., Ph.D.	Other Occupational Needs	5 R18 OH01981-02	130
Clark, William W., Ph.D.	Noise-Induced Hearing Loss	5 R01 OH02128-05	77
Cleary, Stephen F., Ph.D.	Disorders of Reproduction	5 R01 OH02148-05	60
Daniell, William, M.D.	Neurotoxic Disorders	1 R01 OH02683-01	73
DuBois, Arthur B., M.D.	Respirator Research	5 R01 OH02564-02	119
Emurian, Henry H., Ph.D.	Cardiovascular Diseases	1 R01 OH02614-01A1	58
Esmen, Nurtan A., Ph.D.	Control Techniques	2 R01 OH02132-04	97
Evans, John S., Sc.D.	Respirator Research	5 R01 OH02154-02	117
Flynn, Michael R., Sc.D.	Control Techniques	5 R01 OH02392-02	102
Garrett, Carol J., Ph.D.	Traumatic Injuries	5 R01 OH02601-02	52
Garrison, Richard P., Ph.D.	Control Techniques	5 R01 OH02329-03	99
Ghio, Andrew, M.D.	Occupational Lung Diseases	5 R01 OH02264-05	15
Glazer, Eva R., M.D.	Occupational Cancers	5 R01 OH02284-02	41
Goldsmith, David F., Ph.D.	Occupational Lung Diseases	1 R01 OH02726-01	23
Hamernik, Roger P., Ph.D.	Noise-Induced Hearing Loss	5 R01 OH02317-05	79
Hammad, Yehia Y., D.Sc.	Occupational Lung Diseases	1 R01 OH02618-01	21
Harber, Philip I., M.D.	Respirator Research	5 R01 OH02005-06	134
Harber, Philip I., M.D.	Other Occupational Needs	5 R01 OH02288-02	115
Hardy, James K., Ph.D.	Other Occupational Needs	1 R01 OH02651-01	142
Hemstreet, George P., III, M.D.	Occupational Cancers	1 R01 OH02647-01	44
Henderson, Donald, Ph.D.	Noise-Induced Hearing Loss	7 R01 OH01152-09	76
Hinds, William C., Sc.D.	Respirator Research	5 R01 OH01595-05	113
Hjelle, Joseph T., Ph.D.	Other Occupational Needs	5 R01 OH02417-03	139
Jiang, Bernard C., Ph.D.	Control Techniques	5 R01 OH02230-02	98
Karwowski, Waldemar, Ph.D.	Control Techniques	1 R01 OH02568-01	103
Kauffman, Charles W., Ph.D.	Traumatic Injuries	2 R01 OH01122-07A1	50
Leigh, J. Paul, Ph.D.	Other Occupational Needs	1 R01 OH02586-01	140
Leith, David, Sc.D.	Control Techniques	1 R01 OH02437-01A1	102
Levine, Steven P., Ph.D.	Other Occupational Needs	5 R01 OH02303-02	136
Levine, Steven P., Ph.D.	Other Occupational Needs	5 R01 OH02404-02	138
Levine, Steven P., Ph.D.	Other Occupational Needs	1 R01 OH02666-01	144
Mansfield, Phyllis K., Ph.D.	Psychological Disorders	1 R01 OH02162-01A1	93

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Marras, William S., Ph.D.	Musculoskeletal Injuries	1 R01 OH02621-01	35
Merrill, William W., M.D.	Occupational Lung Diseases	5 R01 OH02114-03	12
Nordlund, James J., M.D.	Dermatological Conditions	5 R01 OH02091-05	85
Rappaport, Stephen M., Ph.D.	Other Occupational Needs	5 R01 OH02221-02	133
Rosenman, Kenneth D., M.D.	Occupational Lung Diseases	1 R01 OH02298-01A2	18
Santella, Regina M., Ph.D.	Dermatological Conditions	1 R01 OH02622-01	87
Schachter, E. Neil, M.D.	Occupational Lung Diseases	1 R01 OH02593-01A1	20
Schonfeld, Irvin, Ph.D.	Psychological Disorders	1 R01 OH02571-01	95
Stewart, Walter F., Ph.D.	Traumatic Injuries	5 R01 OH02254-02	51
Stewart, Walter F., Ph.D.	Disorders of Reproduction	1 R01 OH02373-01A1	62
Swanson, G. Marie, Ph.D.	Occupational Cancers	5 R01 OH02067-05	40
Swartz, William J., Ph.D.	Disorders of Reproduction	5 R01 OH00835-11	59
Trudell, James R., Ph.D.	Other Occupational Needs	5 R01 OH00978-09	125
Uyeki, Edwin M., Ph.D.	Other Occupational Needs	5 R01 OH01630-07	128
Venkatasubramanian, Venkat, Ph.D.	Control Techniques	5 R01 OH02352-02	100
Warshawsky, David, Ph.D.	Occupational Lung Diseases	1 R01 OH02277-01A2	17
Willeke, Klaus, Ph.D.	Respirator Research	5 R01 OH01301-06	112
Yoon, Young H., Ph.D.	Respirator Research	1 R01 OH02260-01A2	118
Zellers, Edward T., Ph.D.	Other Occupational Needs	1 R01 OH02663-01	143
Zimmerman, Neil J., Ph.D.	Respirator Research	5 R01 OH01632-02	114

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Bernstein, David I., M.D.	Occupational Lung Diseases	5 K01 OH00073-02	27
Brabdt-Rauf, Paul W., Sc.D., M.D.	Occupational Cancers	1 K01 OH00076-01	45
Conroy, Lorraine M., Sc.D.	Control Techniques	1 K01 OH00078-01	105
Costa, Lucio G., Ph.D.	Other Occupational Needs	5 K01 OH00054-03	145
Crutchfield, Clifton D., Ph.D.	Respirator Research	5 K01 OH00068-03	120
Fenske, Richard A., Ph.D.	Other Occupational Needs	5 K01 OH00063-03	148
Hanna, Linda M., Ph.D.	Occupational Lung Diseases	5 K01 OH00067-03	25
Hodgson, Michael J., M.D.	Other Occupational Needs	5 K01 OH00071-02	149
Murlas, Christopher G., M.D.	Occupational Lung Diseases	7 K01 OH00060-01	23
Parker, David L., M.P.H.	Other Occupational Needs	5 K01 OH00055-03	146
Robinson, James C., Ph.D.	Other Occupational Needs	5 K01 OH00075-02	152
Rogers, Bonnie	Other Occupational Needs	5 K01 OH00072-02	150
Zellers, Edward T., Ph.D.	Other Occupational Needs	1 K01 OH00077-01	153

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Burton, John F., Jr., Ph.D.	Other Occupational Needs	1 R03 OH02550-01	155
Conroy, Lorraine M., Sc.D.	Control Techniques	1 R03 OH02680-01	110
Daniell, William E., M.D.	Control Techniques	1 R03 OH02422-01	107
Hamilton, John D.	Disorders of Reproduction	5 R03 OH02376-02	63
Hopkins, Richard S., M.D.	Traumatic Injuries	1 R03 OH02659-01	56
Leung, Mun-Fai	Dermatological Conditions	5 R03 OH02433-02	88
Lin, Ken C.	Dermatologic Conditions	1 R03 OH02655-01	90
Miller, Glen M., Ed.D.	Noise-Induced Hearing Loss	1 R03 OH02671-01	83

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Murphy, Dennis J., Ph.D.	Control Techniques	5 R03 OH02236-02	106
O'Neil, Carol E., Ph.D.	Occupational Lung Diseases	5 R03 OH02425-02	28
Oestenstad, Riedar K.	Respirator Research	1 R03 OH02580-01	121
Perrino, Brian A.	Other Occupational Needs	5 R03 OH02321-02	153
Punnett, Laura, Sc.D.	Musculoskeletal Injuries	1 R03 OH02689-01	38
Robins, Thomas G., M.D.	Occupational Lung Diseases	1 R03 OH02627-01	29
Savitz, David A., Ph.D.	Disorders of Reproduction	5 R03 OH02548-02	67
Shortridge, Linda A.	Disorders of Reproduction	5 R03 OH02383-02	65
Shy, Carl M., M.D., Dr.P.H.	Occupational Lung Diseases	1 R03 OH02654-01	30
Sorock, Gary, Ph.D.	Traumatic Injuries	5 R03 OH02579-02	53
Spear, Robert C., Ph.D.	Other Occupational Needs	5 R03 OH02555-02	156
Sweeney, Anne M.	Disorders of Reproduction	5 R03 OH02631-02	67
Tseng, Michael T., Ph.D.	Neurotoxic Disorders	5 R03 OH02578-02	74
Twerdok, Lorraine E.	Occupational Cancers	5 R03 OH02632-02	46
Velazquez, Susan F.	Occupational Cancers	1 R03 OH02657-01	48
Wei, Cheng-i, Ph.D.	Other Occupational Needs	1 R03 OH02583-01	157
Wheeler, Donna L.	Musculoskeletal Injuries	1 R03 OH02684-01	36
Wickstrom, Richard J.	Traumatic Injuries	1 R03 OH02653-01	55
Wilkins, John R., Ph.D.	Disorders of Reproduction	5 R03 OH02380-02	64
Zellers, Edward T., Ph.D.	Control Techniques	1 R03 OH02667-01	109

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Benner, Cynthia L., Ph.D.	Other Occupational Needs	1 R43 OH02662-01	158
Roberts, Bruce L.	Respirator Research	1 R43 OH02698-01	123
Stetter, Joseph R., Ph.D.	Respirator Research	5 R44 OH02312-03	122

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Central Institute for the Deaf	William W. Clark, Ph.D.	77
City College of CUNY	Irvin Schonfeld, Ph.D.	95
Colorado Department of Health	Carol J. Garrett, Ph.D.	52
Columbia University	Regina M. Santella, Ph.D.	87
Datachem Laboratories	Young H. Yoon, Ph.D.	118
Duke University Medical Center	Mohamed B. Abou-Donia, Ph.D.	69
Duke University Medical Center	Mohamed B. Abou-Donia, Ph.D.	70
Duke University Medical Center	Andrew Ghio, M.D.	15
Harvard School of Public Health	John S. Evans, Sc.D.	117
Harvard School of Public Health	David C. Christiani, M.D.	20
Louisiana State University Medical Center	William J. Swartz, Ph.D.	59
Virginia Commonwealth University	Stephen F. Cleary, Ph.D.	60
Michigan State University	G. Marie Swanson, Ph.D.	40
Michigan State University	Kenneth D. Rosenman, M.D.	18
Michigan Technological University	Susan T. Bagley, Ph.D.	42
The Mount Sinai School of Medicine	E. Neil Schachter, M.D.	20
Northern California Cancer Program	Eva R. Glazer, M.D.	41
Pennsylvania State University	Phyllis K. Mansfield, Ph.D.	93
Purdue University	Neil J. Zimmerman, Ph.D.	114
Purdue University	Venkat Venkatasubramanian, Ph.D.	100
San Jose State University	J. Paul Leigh, Ph.D.	140
Stanford University Medical Center	James R. Trudell, Ph.D.	125
State University of New York	Donald Henderson, Ph.D.	76
SUNY at Stony Brook	Edward H. Bergofsky, M.D.	18
SUNY - Plattsburgh	Roger P. Hamernik, Ph.D.	79
Texas Tech University	Mohamed M. Ayoub, Ph.D.	32
The John B. Pierce Foundation Laboratory, Inc.	Arthur B. DuBois, M.D.	119
The Johns Hopkins University	Susan P. Baker, M.P.H.	33
The Johns Hopkins University	Walter F. Stewart, Ph.D.	51
The Johns Hopkins University	Walter F. Stewart, Ph.D.	62
The Ohio State University	William S. Marras, Ph.D.	35
The University of Michigan	Charles W. Kauffman, Ph.D.	50
Tulane University School of Medicine	Yehia Y. Hammad, D.Sc.	21
University of Akron	James K. Hardy, Ph.D.	142
University of Arizona	Dean E. Carter, Ph.D.	11
University of California	David F. Goldsmith, Ph.D.	23
University of California	Stephen M. Rappaport, Ph.D.	133
University of California, Los Angeles	Philip I. Harber, M.D.	115
University of California, Los Angeles	Philip I. Harber, M.D.	134
University of California, Los Angeles	William C. Hinds, Sc.D.	113
University of Cincinnati	David Warshawsky, Ph.D.	17
University of Cincinnati	Scott C. Clark, Ph.D.	130
University of Cincinnati	James J. Nordlund, M.D.	85
University of Cincinnati	Klaus Willeke, Ph.D.	112
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University of Maryland	Henry H. Emurian, Ph.D.	58
University of Miami	Shihab Asfour, Ph.D.	34
University of Michigan	Steven P. Levine, Ph.D.	136
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University of Michigan	Steven P. Levine, Ph.D.	144
University of Michigan	Edward T. Zellers, Ph.D.	143
University of Michigan	Richard P. Garrison, Ph.D.	99
University of North Carolina	David Leith, Sc.D.	102
University of North Carolina	Michael R. Flynn, Sc.D.	102
University of Oklahoma	George P. Hemstreet, III, M.D.	44
University of Oklahoma	Nabih R. Asal, Ph.D.	137
University of Pittsburgh	Nurtan A. Esmen, Ph.D.	97
University of Texas Medical Branch	Ghulam A.S. Ansari, Ph.D.	131
University of Washington	Harvey Checkoway, Ph.D.	72
University of Washington	William Daniell, M.D.	73
Virginia Polytechnic Institute	John G. Casali, Ph.D.	81
Wellesley College	Rosalind C. Barnett, Ph.D.	92
Yale University School of Medicine	William W. Merrill, M.D.	12

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Columbia University	Paul W. Brandt-Rauf, Sc.D., M.D.	45
Minnesota Department of Health	David L. Parker, M.P.H.	146
Rush-Presbyterian St. Luke Medical Center	Christopher G. Murlas, M.D.	23
Rutgers University	Richard A. Fenske, Ph.D.	148
The Johns Hopkins University	Linda M. Hanna, Ph.D.	25
University of Arizona	Clifton D. Crutchfield, Ph.D.	120
University of California	James C. Robinson, Ph.D.	152
University of Cincinnati Medical Center	David I. Bernstein, M.D.	27
University of Illinois at Chicago	Lorraine M. Conroy, Sc.D.	105
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University of Pittsburgh	Michael J. Hodgson, M.D.	149
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University of Alabama at Birmingham	Riedar K. Oestenstad	121
University of Arizona	Glen M. Miller, Ed.D.	83
University of California, Berkeley	Robert C. Spear, Ph.D.	156
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University of Cincinnati	Susan F. Velazquez	48
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