Title: Hazard Surveillance in the Defense Nuclear Industry
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Telephone: (310) 206-6141
Award Number: 5 R01 CC912034-03
Start & End Date: 9/30/1995–9/29/1999
Total Project Cost: $1,191,563
Program Area: NORA
Key Words:

Abstract:
The overall goal of this research is to develop an integrated theory, approach, and methodology to exposure assessment and hazard surveillance, which emphasizes characterization of exposure to complex mixtures of chemical toxicants and biomechanical problems as well as single agents. The research has relevance to identification and characterization of problems associated with decommissioning and decontamination of Department of Energy sites, application to the defense nuclear industry and other high-risk industrial locations. This research represents collaboration between the University of California at Los Angeles and Berkeley, Lawrence Livermore and Los Alamos National Laboratories. The specific aims of the overall research can be subdivided into subsections.

1. Exposure assessment and hazard surveillance: To identify appropriate statistical tools for characterizing multiple chemical agents; to explore toxicologic and epidemiologic implications of multivariate exposure characterization; to measure task-specific exposures with real time instrumentation and integrated sampling; to develop models of exposure based on task specific data; to test these models with integrated sampling, and to refine the models based on the results.
2. Modeling pollutant concentration between source and worker: Improve our understanding of small scale (0 to 2 m) dispersion of contaminants with the ultimate goal of predicting personal exposure based on the minimum number of area concentration measurements. To provide a tool for efficient screening of a large number of work sites for potential inhalation hazards.
3. Application of biologic monitoring and biomarkers of exposure for exposure assessment and hazard surveillance: To make use of biologic monitoring, biomarkers of exposure, and toxicokinetic modeling to better estimate internal and target tissue dose from exposure to single and multiple chemical agents and evaluated interactive effects associated with toxicokinetic interaction.
4. Integrated task and postural analysis for ergonomic exposure analysis: To develop, pilot test, and validated an integrated task and postural analysis for ergonomics exposure assessment.
5. Evaluation of current exposure and medical surveillance programs at Los Alamos and Lawrence Livermore National Laboratories: To evaluated the medical and exposure surveillance programs at LANL, identify discrepancies between health and safety "needs" and established monitoring programs, and develop an integrated surveillance

system that efficiently combines hazardous-exposure, biological, and health-outcome monitoring of the worker population.

6. Assessing risks from exposure to multiple physical and chemical agents: To develop and implement a risk based framework and methodology that permits estimation of the incidence of adverse health impact predicted from environmental/biological exposure and enables development of surveillance programs and intervention strategies to prevent adverse consequences of exposures.

Publications

Chen WG, McKone TE: Chronic Health Risks from Aggregate Exposures to lonizing Radiation and Chemicals: Scientific Basis for an Assessment Framework. Risk Analysis, 21, pp 25-42, 2001

Wu JD, Shang N, Hammond SK, Spear RC: Integration and Exploration of Task-Based Exposure Data: Part I: Design of an Exposure Simulator, Am. Ind. Hyg. Assn. J., 2000

Wu JD, Vork K, Spear RC: Integration and Exploration of Task-Based Exposure Data: Part II: Simulation of Solvent Exposures in Raft Manufacturing. Am. Ind. Hyg. Assn. J., 2000

Wu JD, Milton DK, Hammond SK, Spear RC: Hierarchical Cluster Analysis Applied to Workers' Exposures in Fiberglass Insulation Manufacturing. Ann. Occup. Hyg., 43, pp 43-55, 1999

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Centers for Disease Control
and Prevention (CDC)

Memorandum

Date: April 4, 2002

From: Michael J. Galvin, Ph.D., Program Official
Office of Extramural Programs, NIOSH, E-74

Subject: Final Report Submitted for Entry into NTIS for Grant 5 R01 CC912034-03.

To: William D. Bennett
Data Systems Team, Information Resources Branch, EID, NIOSH, P03/C18

The attached final report has been received from the principal investigator on the subject NIOSH grant. If this document is forwarded to the National Technical Information Service, please let us know when a document number is known so that we can inform anyone who inquires about this final report.

Any publications that are included with this report are highlighted on the list below.

Attachment
cc: Sherri Diana, EID, P03/C13

List of Publications

Chen WG, McKone TE: Chronic Health Risks from Aggregate Exposures to Ionizing Radiation and Chemicals: Scientific Basis for an Assessment Framework. Risk Analysis, 21, pp 25-42, 2001

Wu JD, Vork K, Spear RC: Integration and Exploration of Task-Based Exposure Data: Part II: Simulation of Solvent Exposures in Raft Manufacturing. Am. Ind. Hyg. Assn. J., 2000

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WORKER EXPOSURE ASSESSMENT AND HAZARD SURVEILLANCE
FINAL REPORT

1. SPECIFIC AIMS

R01/CCR912034-03

The overall goal of this research is to develop an integrated theory, approach, and methodology to exposure assessment and hazard surveillance, which emphasizes characterization of exposure to complex mixtures of chemical toxicants and biomechanical problems as well as single agents. The research has relevance to identification and characterization of problems associated with decommissioning and decontamination of Department of Energy sites, application to the defense nuclear industry and other high-risk industrial locations. This research represents collaboration between the University of California at Los Angeles and Berkeley, Lawrence Livermore and Los Alamos National Laboratories. The specific aims of the overall research can be subdivided into subsections.

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To evaluate the medical and exposure surveillance programs at LANL, identify discrepancies between health and safety "needs" and established monitoring programs, and develop an integrated surveillance system that efficiently combines hazardous-exposure, biological, and health-outcome monitoring of the worker population.

6. Assessing risks from exposure to multiple physical and chemical agents
To develop and implement a risk based framework and methodology that permits estimation of the incidence of adverse health impact predicted from environmental/biological exposure and enables development of surveillance programs and intervention strategies to prevent adverse consequences of exposures.

Two approaches will be used to organize this final report. For the most part we shall address each specific aim listed above and we shall include manuscripts as appendices. These manuscripts may be published papers, papers under review or in final preparation. Some sections will also have text where a specific manuscript has not yet been prepared.

1. Exposure assessment and hazard surveillance

- **to identify appropriate statistical tools for characterizing multiple chemical agents;**
- **to explore toxicologic and epidemiologic implications of multivariate exposure characterization;**
- **to measure task-specific exposures with real time instrumentation and integrated sampling;**
- **to develop models of exposure based on task specific data;**
- **to test these models with integrated sampling, and to refine the models based on the results.**

Significance of work performed under the NIOSH-DOE Project at Berkeley

There are two significant results from our work, one the identification and specification of the nature of a major unresolved challenge for risk assessment relating to multiple agent exposure and the second significant progress on an approach to the characterization and study of this class of occupational exposures. In particular:

- In our studies of approaches to assessing the cumulative health risks from aggregate exposures to ionizing radiation and chemicals, we found in the literature essentially no guidance for conducting risk assessment for two agents with different mechanisms of action (i.e., energy deposition from ionizing radiation versus DNA interactions with chemicals) but similar biological endpoints (i.e., chromosomal aberrations, mutations, and cancer). Our analysis reveals that this is due to the absence of both the basic science and an appropriate evaluation framework for the combined effects of mixed-agent exposures. This makes it difficult to determine whether there is truly no interaction or somehow the interaction is masked by the scale of effect observation or inappropriate dose-response assumptions. An evaluation framework is proposed.

- In a new approach to characterizing multiple agent exposure, we have developed a computer simulation approach that utilizes both qualitative and quantitiative workplace data for the purpose of both forecasting the complex multivariate nature of these exposures as well as to plan efficient and cost effective exposure measurement and surveillance programs. We feel that this approach circumvents inherently costly approaches based on measurements alone.

Appendix A contains the papers derived from the research associated with this specific aim. The papers are listed here and the numbers in the parentheses following the citation denotes the specific aims to which the work relates.

To date one manuscript describing the work under the grant has been published in a refereed journal, one is in press, two are in the process of being submitted and one is in preparation. The papers are:

Hierarchical Cluster Analysis Applied to Workers' Exposures in Fiberglass Insulation Manufacturing, J.D. Wu, D.K. Milton, S.K. Hammond and R.C. Spear, Ann. Occup. Hyg., 43, pp 43-55, 1999. (1, 2)

Chronic Health Risks from Aggregate Exposures to Ionizing Radiation and Chemicals: Scientific Basis for an Assessment Framework, W.G. Chen and T.E. McKone, Risk Analysis, 21,pp 25-42, 2001. (2)

Integration and Exploration of Task-Based Exposure Data: Part I: Design of an Exposure Simulator, J.D. Wu, N. Shang, S.K. Hammond, and R.C. Spear, In review, Am. Ind. Hyg, Assn. J., 2000 (4)

Integration and Exploration of Task-Based Exposure Data: Part II: Simulation of Solvent Exposures in Raft Manufacturing, J.D. Wu, K. Vork, and R.C. Spear, In review, Am. Ind. Hyg, Assn. J., 2000 (3, 4)

Evaluating the Attributes of Incomplete Data on Workers' Exposure to Benzene; A CART Analysis, W.G. Chen, S.K. Hammond and T.E. Mckone, In preparation (2)

To date four papers have been presented at national meetings on the outcome of work sponsored under the grant:

Simulation of Occupational Exposures to Mixtures, J.D. Wu, Intl. Soc. of Exp. Anal. Annual Meeting, Research Triangle Park, November 1997;

Risks for Workers Exposed to Mixed Physical and Chemical Agents: Benzene and Radiation Case Study, W.G. Chen, T.E. McKone and R.C. Spear, Soc. for Risk Anal. Annual Meeting, Washington D.C. December 1997.

Biological Monitoring to Assess the Health Risks for Workers Exposed to Mixtures of Chemical and Physical Agents, W.G. Chen, T.E. McKone and R.C. Spear, Am. Ind. Hyg. Conf. And Exposition, Atlanta, GA, May 1998

Exploring the Use of Simulation as a Tool for Workplace Exposure Assessment, Shao-wen Liaw, Katharine Hammond, Robert C. Spear, Jyun-De Wu, and Mark Nicas, Am. Ind. Hyg. Conf. And Exposition, St. Louis, MO, May 1999

We are pleased with our accomplishments in meeting four of these five aims. We made a number of attempts to locate a DOE site in which decommissioning and deconstruction work was underway and where we could pursue the fifth aim of testing our modeling and methods development work, but without success. At one time or another we had conversations with individuals from Los Alamos, Livermore, and Savannah River, with some discussion regarding Hanford, but for one reason or another things never worked out. Indeed, we had hoped to work at a DOE site in our earlier work relating to aim 3, but were frustrated in that as well and chose to work in a commercial plant.

2. Modeling pollutant concentration between source and worker
Improve our understanding of small scale (0 to 2 m) dispersion of contaminants with the ultimate goal of predicting personal exposure based on the minimum number of area concentration measurements. To provide a tool for efficient screening of a large number of work sites for potential inhalation hazards.

William Hinds and Bart Ashley

Near-Field Dispersion Modeling
Abstract:

This component of the project addresses the development of a screening tool for hazard surveillance in the defense nuclear industry, including decommissioning and decontamination. The approach evaluated here is the development of an indoor, nearfield dispersion model for estimation of exposure concentration based on source strength and worker location for typical indoor spaces. This report presents the results of a literature search, the use of a three-axis sonic anemometer to characterize turbulent mixing, and estimate eddy diffusion coefficients, and the development of experimental designs and models to estimate to near-field (0 to 3 meters) concentrations within indoor environments. The results of the literature search indicate that there has been little research conducted into the development of near-field dispersion models. Related topics were identified that may prove useful during the development and validation of a near-field dispersion model. These papers cover a wide range of applications that include massbalance models to estimate contaminant concentrations arising from industrial emissions, numerical analysis methods to characterize contaminant dispersions, and topics relating to the design of experiments to characterize air motion within an enclosed space. The results of the use of the three-axis sonic anemometer indicate that is useful technique to characterize turbulent mixing, and estimate eddy diffusion coefficients within the indoor environment. The use of three-axis sonic anemometry data coupled with a serial correlation data analysis program has proven successful at differentiating indoor environments with different levels of turbulent mixing, (e.g. wind tunnel at 1 m/s versus normal laboratory environment). The three axis sonic anemometer data coupled with a defined angle range data analysis program estimated eddy diffusion coefficients for different levels of turbulent intensity. Several experimental designs have been developed which utilize three-axis sonic anemometry data to estimate near-field concentrations. Experimental measurement of concentration as a function of distance from a point source allowed the development of a simple power function model to predict concentration up to 1 m from a source in a laboratory setting.

Specific Aims
The specific aim for this component (modeling concentration between the source and the worker) of the study, as stated in the proposal, is: "To improve our understanding of small scale (0 to 2 m) dispersion of contaminants with the ultimate goal of predicting personal exposure based on the minimum number of area concentration measurements. To provide a tool for efficient screening of a large number of work sites for potential inhalation hazards.

Background And Significance
Background: Hazard surveillance includes the assessment of the occurrence and distribution of the hazards associated with exposure to chemical agents as a means of preventing adverse outcomes. Because of the high potential for chemical exposure at DOE sites, including decommissioning and decontamination, there is a need for screening tools that can identify those exposure situations that have high potential for overexposure to chemicals. This component of the project addresses one such screening tool, the estimation of exposure concentration, based on source strength and the physical location of the worker relative to the source, through the use of indoor, near-field dispersion models.

Currently there is limited understanding regarding how the average concentration of an airborne contaminant changes with distance from the generating source in the near-field (0-3 meters) of an indoor environment. The development of a near-field dispersion model that is capable of estimating airborne concentrations at different locations from a generating source would be valuable in identifying and estimating workers at risk of inhalation exposure in the workplace. Near-field dispersion models could serve as a screening tool to evaluate a large number of workplaces for potential inhalation hazards. The most useful near-field dispersion model would be able to predict potential personal inhalation exposures based on a minimum number of area concentration measurements. The results of the near-field dispersion estimates would allow for maximizing the value of limited air sampling resources to identify changes in workplace exposures or processes that may result in higher exposures to workers.

The type of input data required for near-field models depends on whether the generating source is continuous or intermittent. To utilize a near-field model for a continuously generating source the exposure geometry, air velocity distribution and source strength or average room concentration of the contaminant must be determined. The average room concentration for a reasonable well-mixed room can be determined readily by measuring the average concentration of the contaminant over a period of time at the exhaust duct for the room (Hinds, 1995). Assessment of the exposure geometry requires analysis of the location of the generating source relative to the worker and requirements of the task being performed by the worker. Characterization of air velocity in the room is a more involved task that requires measuring the air velocities at different locations within the room and a determination of the amount of mixing that takes place as a result of the air motion. For intermittent generation sources the near-field model would require knowing the amount of contaminant generated per unit time or the amount of contaminant generated per unit operation and their duration and the exposure geometry and air motion characteristics.

The accuracy of a near-field dispersion model for an indoor environment is dependent upon the characteristics of the air motion within that space. Currently the air motion characteristics of an indoor environment are incorporated into a mixing factor. The mixing factor is used to estimate the effect of incomplete mixing upon the potential contaminant concentration. In effect the K factor is a general purpose safety factor which is used to account for, among other things, the fact that mixing within an indoor environment is not complete. The K factor is based on several considerations: 1) the efficiency of mixing and distribution of replacement air introduced into the room or space being ventilated; 2) the toxicity of the airborne contaminant; 3) other factors such as duration of the process, operational cycle, location of workers relative to sources of contaminants, location and. number of generation points within the workplace, seasonal changes in the amount of natural ventilation and possible reduction in the operating effectiveness of mechanical air moving devices (ACGIH, 1995). After evaluating these considerations the K factor value selected generally ranges from 1 to 10. A potential problem with the use of the K factor arises from the fact that many of the criteria that are used to estimate the K factor are based on professional judgment. Because professional judgment is widely variable a more quantitative estimate of the amount of mixing is desired. The use of a three-axis anemometer provides a quantitative measurement of the amount of mixing that occurs within an indoor environment.

A. Literature Search

A literature search was completed for topics relating to near-field dispersion models. The Results of the literature search indicate that there has been little research into the development and evaluation of near-field dispersion models. During the course of the literature search several related research topics were identified that may prove useful in the development of near-field dispersion models. The majority of the literature that relates to the study of contaminant dispersion can be grouped into one of three categories: (1) model development and analysis based on emission rates, (2) room mixing research, and (3) data analysis methodologies. The relevant publications for each category are discussed below.

Model Development

Brief, R.S., et. al., published a paper entitled "Development of exposure control strategy for process equipment.," which discussed the need to evaluate near-field dispersion models in order to estimate the expected emissions resulting from process equipment failures, such as leaking seals and gaskets in the petroleum industry. The near-field dispersion equation described in their paper needs to be validated in a controlled laboratory environment to determine its accuracy in predicting contaminant concentrations in the near-field.

Six papers have been published by Wadden, R.A., and co workers, which describe methods to quantify indoor contaminant concentrations in terms of emission factors and emission rates. Emission rates are the mass of pollutant released per unit time and the emission factor is the mass of pollutant released per unit of source activity. The benefit of generalizing contaminant concentrations in terms of emission rates and emission factors is that the results can be applied to other spaces or environments that contain the same type of pollution sources and processes (Wadden, et. al., 1994). Emission rates are determined by measuring the area concentration patterns surrounding each pollutant generating device while production is taking place. An emission rate is calculated from a mass-balance model which relates measures of source activity, process conditions and equipment geometry. Several papers relating to the development of emission factors are briefly described below.

Wadden, et. al. (1994) discussed the determination of emission rates for ethyl alcohol resulting from a candy glazing operation. The emission rates were translated into emission factors by relating them to observations of source activities. The investigators used a combination of mass balance modeling approach and on-site field testing to determine that the ethanol emission rate was between 38.4 kg/hour and 49.6 kg/hour. The emission factor was determined to be between 291 grams ethanol/batch of candy to 500 g/batch. The investigators reported that the calculated emission data was in agreement with the estimate of 446 g/batch based on the glaze mixture composition and the amount of glaze mixture added to each batch of candy. An one-compartment completely mixed space mass-balance model was used to transform the area concentration measurements to emission rates.

Wadden, et. al. (1991) used two different mass-balance models to estimate emission factors for trichloroethylene degreasing operations. The authors used a Multi-Point Eddy Diffusion mass-balance model to determine the emission rates when one pollution source is the major contributor to concentrations in the surrounding space. This model assumes a hemispherical space and neglects surface deposition effects (Wadden et. al., 1991). The authors used a Completely Mixed mass balance model in the case where many sources make significant contributions to area concentrations. The Completely Mixed mass balance model was used under the assumption that the workplace approaches the conditions of a completely mixed container. This model also neglects the effects of reaction and surface deposition.

Conroy, et. al. (1995) described the use of the Multi-Point Eddy Diffusion model to determine the emission rates and emission factors for a chromium plating operation. The authors reported a emission factor of 2.6×10^{-4} mg chromium/A•hr.

Wadden, et. al. (1995) utilized a Completely Mixed Space Mass Balance model (Analytical Approach) described previously and the Experimental Mass Balance Approach to determine the emission rates and emission factors for volatile organic compounds in a sheet-fed offset printing operation. The authors reported a correlation coefficient, r^2=0.55 between measured and predicted concentrations for the Experimental Mass Balance equation and a correlation coefficient, r^2=0.46 between measured and predicted concentrations for the Completely Mixed Space Mass Balance equation.

Liao, et. al. (c.a. 1995) utilized a Chemical Mass Balance model to estimate copper and chromium emissions in an electroplating shop. The authors used a weighted-least squares technique to solve the equation for source coefficients. The weights used were the reciprocal of the measured concentration squared (1 /conc^2). The authors reported that the Chemical Mass Balance model explained 100% of the variations in copper concentrations measured at three locations in the copper plating shop, with contributions of 95-98% attributable to the plating line. The CBM model explained 100% of the variations in chromium concentrations measured at four locations in the plating shop.

Scheff, et. al. (1992) compared a Box model and an Advective-Diffusion model to translate area concentration measurements to emission rates for open-top vapor degreasers. Freon concentrations were measured using both charcoal-tube/gas chromatographic and Tedlar bag/infrared absorption methods. The box model assumes that rapid mixing occurs throughout the box, the system is steady state and the air velocity and pollutant emission rates are constant. The authors reported that the average emission predicted by the box model for the six hours with bag and charcoal-tube data was 74 g/hour, which was close to the 95 g/hour predicted by the advection-diffusion model for the same hours. The correlation between the two models for these six hours was 0.91.

Jaycock, et. al. (1995) evaluated the use of a ,simplified concentration model which requires only source rate and saturated vapor concentration as experimentally derived inputs. Airborne exposure models were developed to account for volatilizing sources and adsorbing surface sinks of isothiazone biocide volatilized from treated wood into glass chambers and real-world environments. The authors reported that the model provided acceptable accuracy in that it overestimated measured room concentrations in two tests to within a factor of 2-4. The investigators also found significantly lower equilibrium concentrations in a real room environment compared to a glass test chamber.

Keil, (1998) completed field studies to develop and evaluate toluene emission factors for a parts-washing operation. The author used a mass-balance model that divided the airspace into near and far fields of exposure concentrations. Near field concentration measurements were taken at 0.3 meters and 0.6 meters from the source. Far field concentrations were measured at a 12 and 24 meters from the source and represented the average room concentration. The author reported good correlation between the predicted toluene concentration estimates and the measured concentrations (slope=1.1, r^2=0.66, $p<0.05$).

Drivas, et. al. (1996) proposed a simplified analytical indoor model that describes the concentrations as a function of position and time in a room following a short-term release of particles and gases. The indoor dispersion model considers point-source dispersion with wall reflection and general room concentration decay due to deposition and room ventilation. The authors reported excellent agreement between model predictions and experimental results conducted by other researchers.

Room Mixing

Gonzales, et. al. (1974) investigated the relationship between fixed aerosol samplers and breathing zone air sampling measurements. The authors utilized dioctylphthalate as a tracer aerosol and measured aerosol concentration throughout the work area, with different ventilation rates. The results indicated that aerosol concentrations in the worker's breathing zone was up to 250 times greater than concentrations which might be indicated by typical fixed room-air samplers located adjacent to the glove box. General ventilation conditions (room air changes per hour and air direction relative to the leak flow) were varied. Under all ventilating conditions the highest aerosol concentrations were close to and in front of the leak source.

Nicas, M. (1996) investigated the potential error in exposure estimates that may occur due to use of the well-mixed room model. The author reported that use of the well-mixed room model may lead to an underestimation error of worker exposure intensity, up to 40%. The author presents a methodology for estimating ventilation efficacy using realtime measurements at the worker location and room exhaust, coupled with room exhaust rate.

Rigsbee and Perkins (c.a. 1995) investigated the variability in the K factor values based upon worker location and turbulence intensities. The authors reported that based on the results of experimental data the ACGIH recommended K factor may only be applicable to a few workplace locations. This study also reported that as the generation rate increases and the exhaust flow rate increases, the average K factor and K factor variance increases, and K factor variances are lowest in turbulent conditions.

Data Analysis Methodologies

Madsen, et. al. (1996) investigated the relationship between several aerosol parameters (particle diameter, density, and initial velocity) and their influence on aerosol dispersion and capture by a local exhaust. A numerical model based on the Langrangian method was used to estimate the motion of a spherical, rigid particle in a fluid flow system. Computational fluid dynamic software (EOL) was used for the numerical simulations. The authors reported that numerical method used in this study is capable of handling the complex system of contaminant sources in the industrial environment.

Nabar, et. al. (1996) investigated the use of computational fluid dynamics (CFD) to evaluate experimental and simulated air mixing for dilution ventilation of confined spaces. Using residence time distributions (RTD), two air mixing parameters were defined and computed for physical experiments and computer simulations. The authors concluded that CFD simulations of ventilation experiments using commercially available software were reasonably consistent with physical experiments and RTD-based mixing parameters were useful in evaluating air mixing in physical experiments and computer simulations.

Rodes, et. al. (1995) investigated experimental considerations for conducting controlled studies of the dispersion of contaminants near a mannequin. In addition the authors identified the need to develop realistic respiratory systems in the mannequins.

Literature Search Discussion:

Based on the results of the literature search the use of anemometry data to describe turbulent mixing is a technique which has not previously been applied. Many of the papers that were identified during the course of the literature search are useful in developing experimental methods to describe air motion in indoor environments.

Of particular interest are the papers which describe the use of computational fluid dynamics, which can be used as a comparison against experimentally obtained results. The use of computational fluid dynamic methods appears to be a sophisticated technique that may yield valuable insight when properly applied.

The mass-balance models presented by the research group at the University of Illinois at Chicago may prove to be useful if eddy diffusion data can be estimated from the anemometer data to describe the air motion within a room. Presently these models utilize very limited air motion data to characterize the contaminant dispersion resulting from industrial processes such as chrome plating and sheet-fed printing. The attempt to quantify the mixing factors by Rigsbee and Perkins, and the work of Nicas are useful papers which may provide some helpful experimental methods which may be used in the future during further research on turbulent mixing and the role of eddy diffusion in contaminant dispersion.

Keil, (1998) has proposed a near field dispersion model that accounts for the concentration differences between the near and far fields. This method uses a mass balance model that defines a near field transport coefficient for concentrations from 0.3 to 0.6 meters from the source and a far field coefficient for concentrations from 12 to 24 meters from the source. This model would be improved by adding more comprehensive data regarding the air velocity distributions from the 3-axis sonic anemometer characterizations of air velocity distributions. The anemometer data allows for the calculation of the mean velocity, duration of coherent segments, and the net displacement for all segments. This information could then be utilized to determine eddy diffusion coefficients for both near and far fields.

B. Development of theoretical dispersion models

Three-Axis Sonic Anemometer:
An Applied Technologies 3-Axis Sonic Anemometer, Model SAT-211/3Vx was used to determine the efficacy of using anemometry data to describe air motion characteristics of different indoor environments. The sonic anemometer is capable of measuring wind velocities in three orthogonal axes (u, v and w) and sonic temperature. The sonic temperature is used to calculate the speed of sound at the temperature of operation. In the current data collection set-up the a and v axes are horizontally aligned and the w axis is vertically aligned. The sonic anemometer is composed of a probe array, whose sonic transducers are separated by 15 cm (Applied Technologies, 1995). Sonic pulses are generated at the transducers and are received by opposing transducers. By measuring the transit times, t, and t2 in opposite directions on the same sound path (axis), Vd (velocity parallel o the sound path) can be determined.

Serial Correlation Method
The data from the anemometer are collected using a 586 100 MHz laptop computer equipped with Pro Com Plus data collection software. The collected data are analyzed using a Turbobasic computer program which calculates the rms velocities (m/s) with standard deviations, along the three axes for the sample period. After the rms velocities are calculated the data analysis program computes 500 serial correlations. Serial correlations are used to determine how the wind speed of a particular axis at time t, relates to the speed at t2, t3, t,, , where n is equal to 500. The 500 serial correlations are based on the first 50 seconds of the data run. Anemometer measurements are collected at a point within a room or other indoor space and the rms air velocity along each of the three axes determined. A characteristic turbulent signature is obtained from these data by calculating serial correlation coefficients for lag times of 0.1 to 50 seconds. The serial correlations determine how a velocity measurement at t, relates to subsequent measurement at t2, t3, t4, t, where tX - t, is the lag time and x is equal to 2, 3, 4 n. The decay of correlation with lag time reflects the decay of temporal and spatial coherence of the instantaneous air motion and is the key to estimating eddy diffusion coefficients from anemometry data. This method has proven successful at differentiating indoor environments with different levels of turbulent mixing.

Defined Angle Range Method

The current data analysis program is designed to determine the velocity vector (speed and direction) of the air motion within the environment being measured, every tenth of a second. The program first removes the systematic velocity components to leave only the random velocity component, for each of the three axes. The program then analyzes the set of random velocities to determine the direction and average velocity for each period in which the velocity is reasonably constant in direction. Each such period is considered a coherent velocity segment and its attributes stored. The range of angles to be included in a segment is under control of the investigator. When this analysis is complete the mean velocity, duration, and the net displacement for all segments are calculated. These data are used to estimate eddy diffusion coefficients by the equation given below.

Eddy Diffusion Coefficients Analogous to Molecular Diffusion

Based on the results of the 3-axis anemometry measurements within the wind tunnel and laboratory environments it appears that the use of anemometry data to describe the air motion characteristics of indoor spaces is a promising technique. The 3-axis anemometer data coupled with the serial correlation data analysis program provides a means of differentiating the amount of turbulent mixing that is present in an indoor environment. In addition the delay time which corresponds to a serial correlation value can also be used to estimate the eddy diffusion coefficient at the point of measurement. If eddy diffusion is characterized in terms similar to molecular diffusion the eddy diffusion coefficient can be estimated by the following process. Hinds (1999) gives molecular diffusion coefficient as,

$D = 1/3\ \bar{c}\,\lambda$ where: D = molecular diffusion
$\bar{c}$ = mean thermal velocity
λ = mean free path

By analogy to molecular diffusion and neglecting any systematic velocity component:

$D_e = k(\bar{u}')\,L_e$ where: D_e =eddy diffusion
k = empirically derived constant
$\bar{u}'$ = rms velocity in the u-axis
L_e = distance air parcel travels during time t, see below
$L_e = (\bar{u}')(t_c)$
where t_c is the time over which displacement is correlated (e.g. delay time for a correlation of 0.5)

$D_e = k\,(\bar{u}')(\bar{u}')\,t_c = k(\bar{u}')^2\,t_c = k[(m/s)(m/s)(s)] = m^2/s$

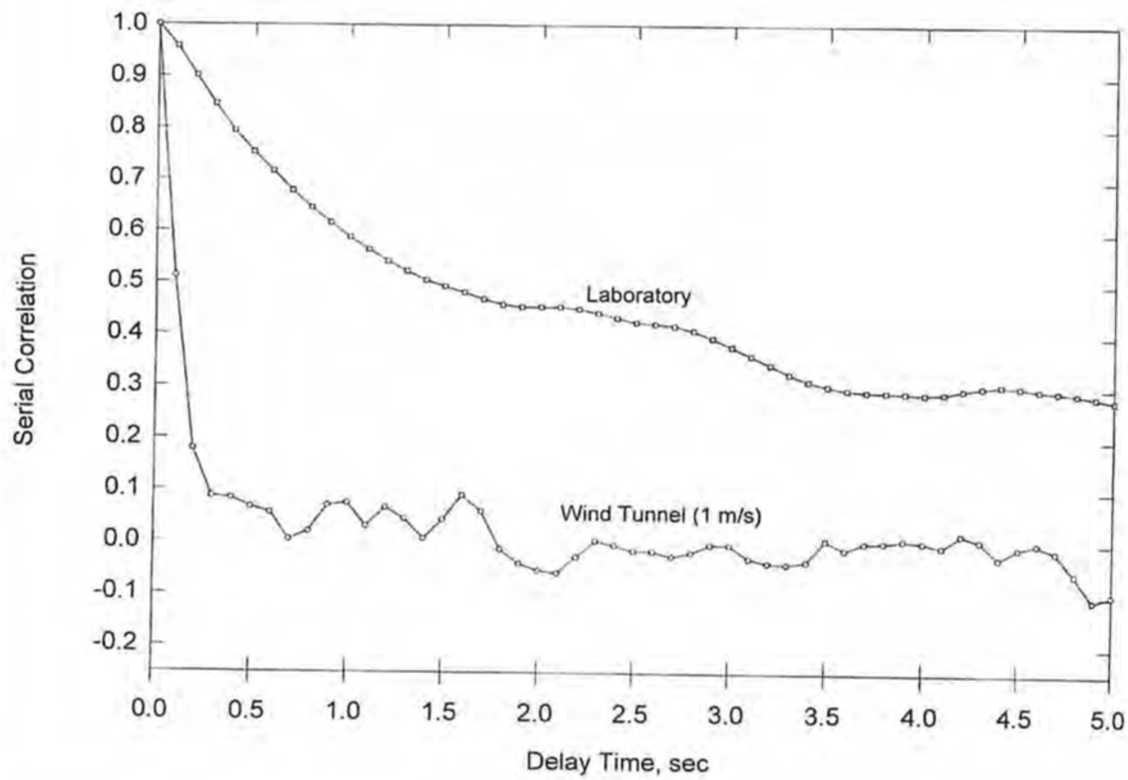
Characterization of laboratory and work stations in terms of distribution of air velocities.

Experimental Results:

Using the serial correlation method described previously the sonic anemometer was able to distinguish between the laboratory and wind tunnel environments.

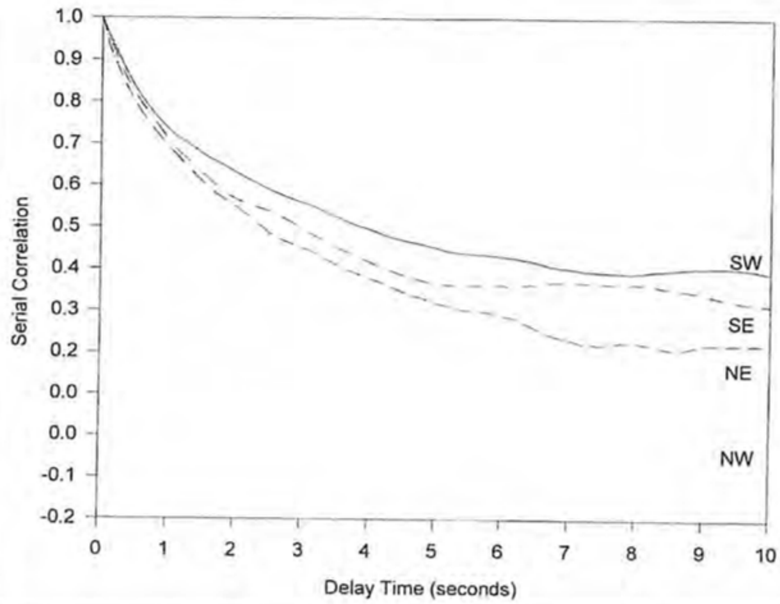
Using the serial correlation data analysis program the three axis sonic anemometer was used to characterize two indoor environments with different turbulent mixing characteristics as shown in Figure 1. The anemometer was placed within a wind tunnel with a 1 meter per second horizontal velocity and in a laboratory. As expected the results show that the correlation of the velocity component lasts for a longer period of time in the less turbulent laboratory environment than in the wind tunnel. In the wind tunnel environment the serial correlation drops to 0.5 in less than 0.25 seconds. It takes approximately 1.5 seconds for the serial correlation to reach 0.5 in the less turbulent laboratory environment.

Figure 1: Serial Correlations for Two Environments



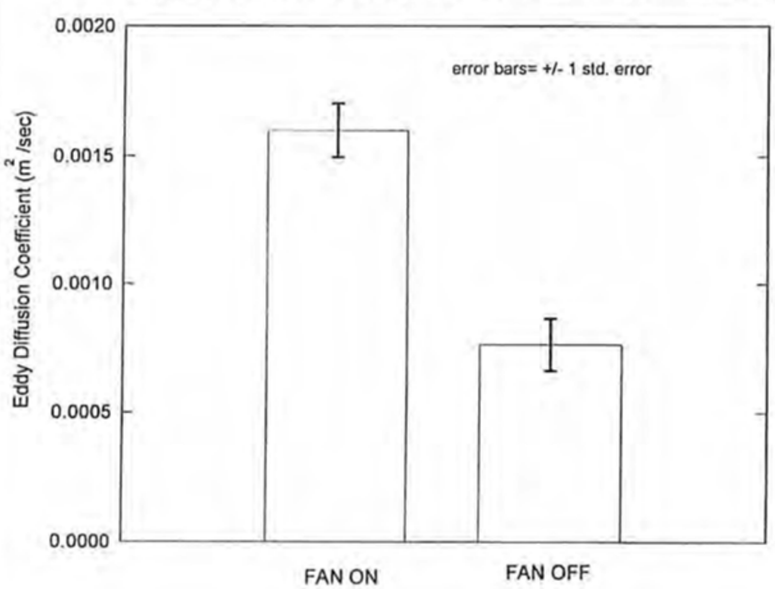
A subsequent investigation into differentiating indoor environments was to characterize the turbulent mixing characteristics at four locations with the sonic anemometer within a laboratory environment. The serial correlation data analysis was then used to determine any differences in the turbulent mixing characteristics at four different locations within the laboratory. As shown in Figure 2 there are differences in turbulent mixing characteristics within the laboratory. The time required to reach a serial correlation of 0.5 ranged from approximately 2.0 seconds to 4.0 seconds. The longer delay times to reach a 0.5 serial correlation indicate a lower turbulent intensity and slower mixing.

Figure 2: Serial Correlation vs. Delay Time in Laboratory Environment



Using the three axis sonic anemometer and the Defined Angle Range data analysis method eddy diffusion coefficients were calculated within the laboratory. An air- circulating fan was placed within the laboratory to create greater turbulent intensity. As shown in Figure 3 the eddy diffusion coefficients calculated with the fan operating are significantly larger than those calculated with the fan off.

Figure 3: Effect of Fan on Eddy Diffusion Coefficients



Validation and improvement of local dispersion models in the laboratory

- Computer Data Analysis

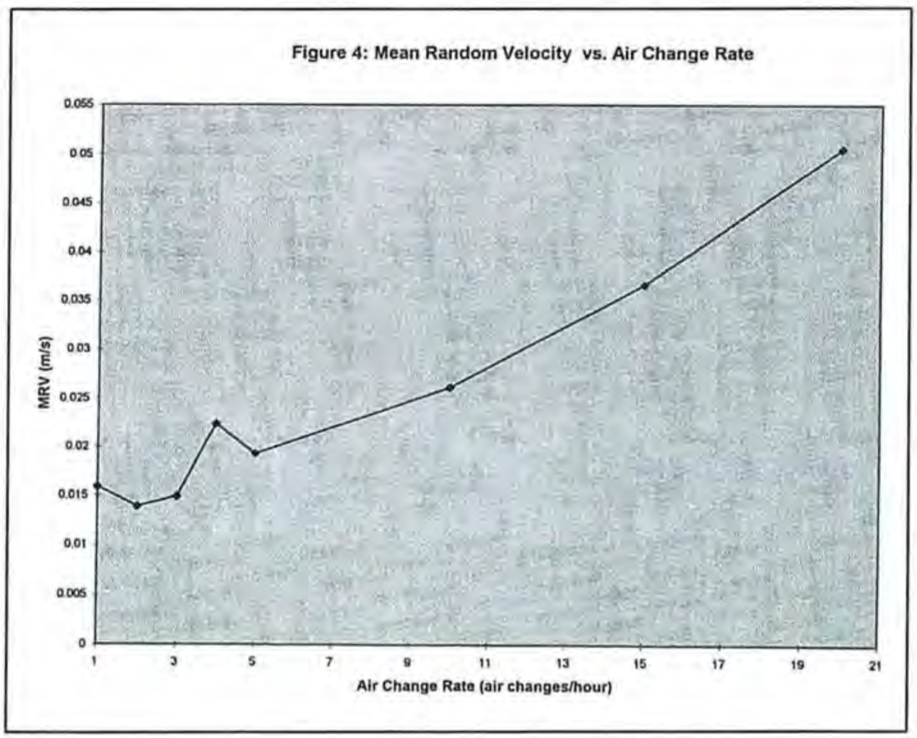
Characterization of laboratory work stations using the three-axis sonic anemometer has been completed in a mechanically ventilated laboratory. The sonic anemometer records the air velocity in 0.1 second intervals, along each of the three axes. A computer program is then used to reduce the data, calculate the systematic and rms velocities in each axis. The computer program then checks the data for transmission errors, allows removal of background anemometry data, and permits selection of any portion of the full data file.

- Rochester Chamber Results

Our attempts to establish known eddy diffusion coefficients in a modified 0.4 m3 Rochester exposure animal exposure chamber were unsuccessful due to the formation of convection cells in the chamber. This gave nonuniform mixing in the chamber so it could not be used to validate our prediction based on anemometry data, using the defined angle range method described previously, not be used to determine the turbulent intensity within the chamber. Several experimental results were verified with the Rochester chamber despite the nonuniform mixing.

Experimental Results:

Despite the formation of convection cells within the Rochester chamber, it was possible to confirm that as the air change rate increased the mean random velocity calculated by the defined angle range method data analysis program increased as well. This was expected and seen in Figure 4.



E. Acetone Generation System

A steady-state acetone generation system was developed to generate known concentrations of acetone vapor shown in Figure 5. The acetone vapor is generated by passing a compressed air stream at known flow rate through two flasks, in series, filled with liquid acetone. This stream is then mixed with a dilution air stream to achieve the desired concentration of acetone vapor. The acetone vapor exits the generating system via a porous 2.5 cm diameter ball. After exiting each flask the vapor stream flows through a 6-mm ID copper tube approximately 4 m long. This allows thermal equilibrium between the vapor stream and the ambient environment to within 1 K. A temperature probe is used to measure the temperature of the acetone vapor prior to leaving the generating system. The concentration of acetone vapor is then measured at different locations from the 2.5 cm ball, using a PE Potomac 2020 Photo ionization Air Monitor (PAM). Monitoring of the concentration of acetone vapors is achieved by mounting the PAM on a laboratory ring stand which can be placed at locations surrounding the ball. Measurements were made over the range of 0.1 to 1,700 p.m., a range found to be linear within five percent by calibration.

Uniformity of acetone vapors leaving the system through the 2.5 cm ball was confirmed by monitoring the concentration of acetone vapors at 6 positions on the surface of the ball. The concentration values obtained indicate that the acetone is released in a 360 degree sphere, which is then acted upon by the prevailing air motions within the laboratory. A smoke tube was added to the system during these investigations to provide visual confirmation of the concentration data obtained from the PAM. Data characterizing concentration decay as a function of the distance from the source were obtained by three dimensional concentration measurements in the vicinity of the porous ball (0 to 1 m) acetone emitter in a laboratory environment.

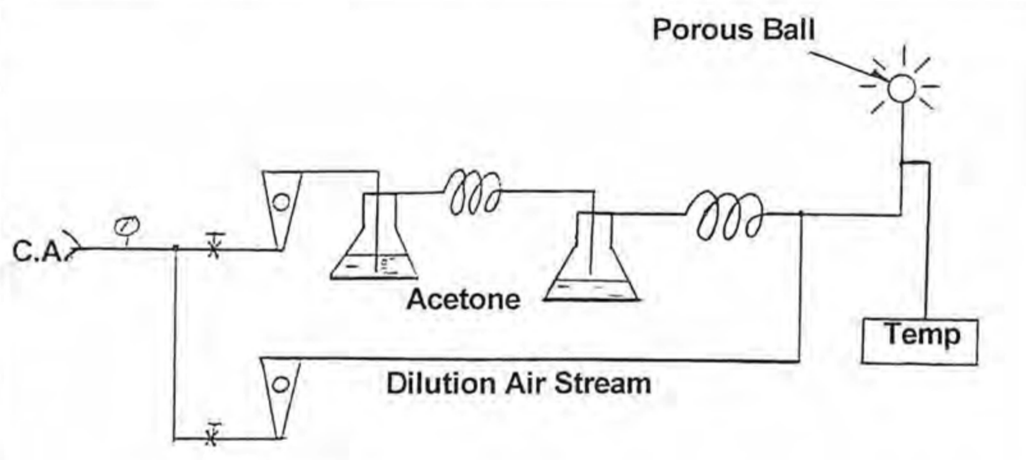


Figure 5. Schematic Diagram of Acetone Generator

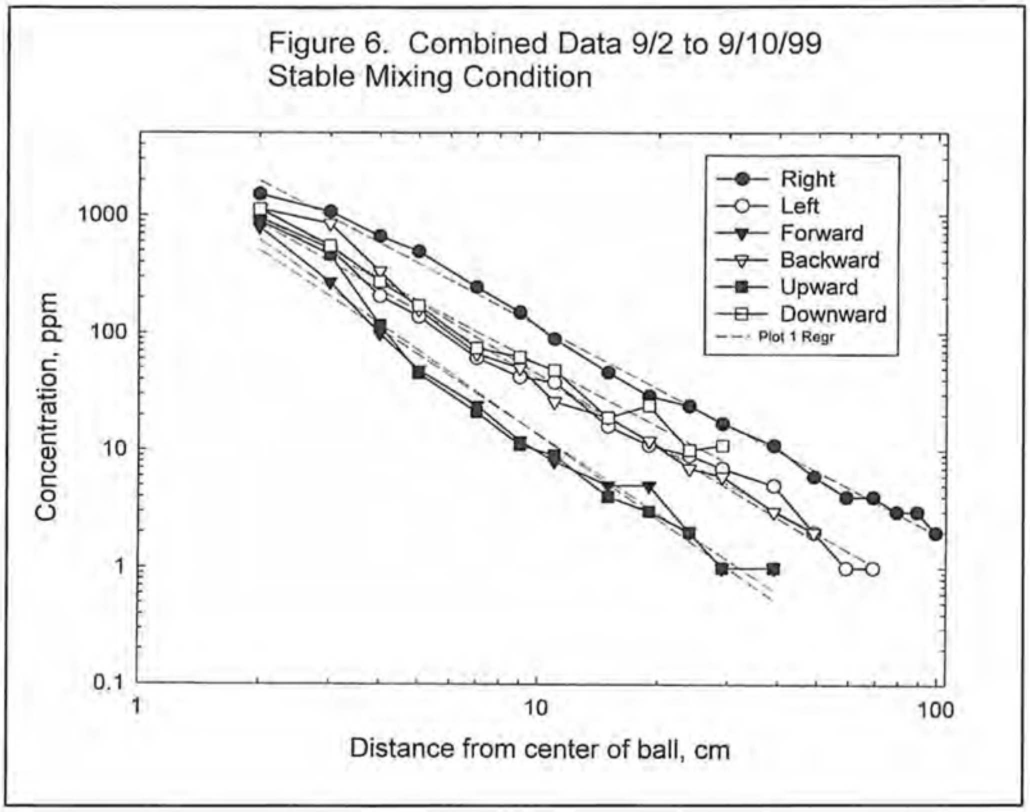
Density of the acetone vapor
The density of the acetone vapor generated was calculated based on the flow rates of acetone vapor and dilution air stream and temperature of the stream prior to leaving the ball. The density of the acetone vapor was compared to vapor-free air for a range of possible laboratory temperatures. This information is required to eliminate the possibility that buoyancy effects may be affecting the transport of the acetone vapor. A smoke tube was added to the vapor generating system for these investigations. The qualitative results from the smoke tube runs indicate that the relative buoyancy of the acetone vapor leaving the system can be predicted based on flow rates and the temperature of the airstream. This was confirmed qualitatively with the smoke tubes.

The porous ball was located 35 cm above a standard lab bench and 28 cm back from the front edge of lab bench. The bench is 56 cm deep from the front edge to the open shelves at the back. The shelves extended 1 m above the bench. Concentration measurements were made along three octagonal axes (six directions away from the ball). Average concentration measurements were made over five-minute intervals at 18 positions from 2 to 99 cm from the center of the ball in all six directions. The directions are labeled as one would when facing the lab bench, right, left, forward (towards the edge), backwards (away from the edge), and upwards and downwards.

Two levels of mixing were evaluated. One was termed "stable", representing a laboratory environment with no human activity. The only air motion was that due to room ventilation from overhead supply and exhaust ducts. This is the environment characterized by line NE in Figure 2. The second mixing stability condition is typical of moderate activity in a laboratory setting, It was simulated by using the same conditions as for the stable condition described above, but with the addition of a person walking by every 30 seconds. The person walked at 2 m/s as close to the counter edge as possible, and alternated directions. Her shoulder was approximately 33 cm from the ball.

Seven replications of the stable condition were made and four replications were made for the moderately active condition. Measurements were made out to 0.99 m in all directions, except where there was a physical constraint or concentrations were not detectable by the PAM, 0.1 p.m.

Results for the stable condition along all six directions are shown on a log-log plot, Figure 6. Also shown is the least squares best fit line for each direction. The decay with distance from the center the ball shows a good fit to a straight line on the log-log graph. The slope for the lines shown ranged from -1.77 to -2.38 with an average value of - 2.02 and a standard deviation of 0.25. The lines show of best fit show a 20-fold range in concentration at a distance of 0.5 m, with the right direction having the largest concentration at any given distance. The upward direction and the forward direction showed the steepest slope, indicating the most rapid decrease in concentration with distance. The other directions show intermediate decay rates.



These results are consistent with two factors that affect decay of concentration with distance, prevailing air motion and openness or absence of reflecting services. The concept of prevailing air motion direction requires elaboration. It is not the usual direction of the wind, where wind is going in one direction with fluctuations in the magnitude of the wind velocity. Rather, it is air motion that goes in all directions, first one-way and then the other, but goes more often in the direction of the prevailing air motion direction. Here the fluctuations are much greater than the average velocity in contradistinction to the usual situation with wind.

Reflecting surfaces such as the lab bench restrict the size of eddies and reflect concentrations at the surface, that is they do not allow concentration to decay into the surface. Both the prevailing direction and reflecting surfaces have the effect of reducing the rate of decay with distance from the source. In this setup the prevailing air motion direction due to room ventilation was to the right along the bench.

Figures 7a to 7c show decay of concentration for both directions along each of the axes. Also shown are error bars (t one standard deviation). Although there is scatter in the points there is no indication that concentration is not following a straight line on the loglog plot of concentration vs. distance from the center of the ball.

Figure 7a Combined Data 9/2 to 9/10/99

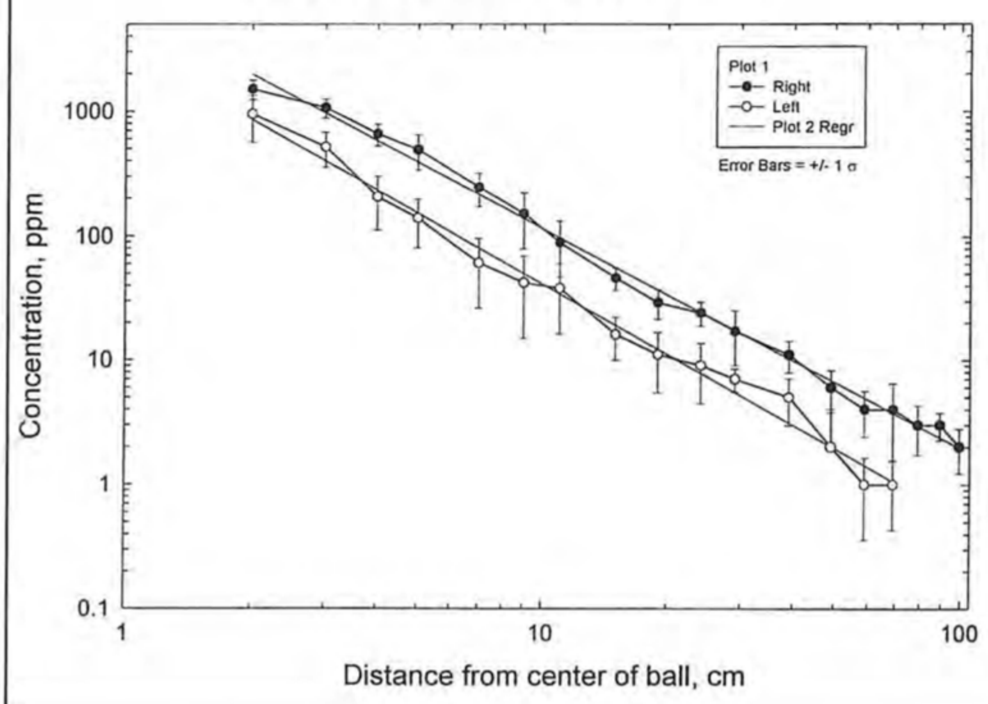
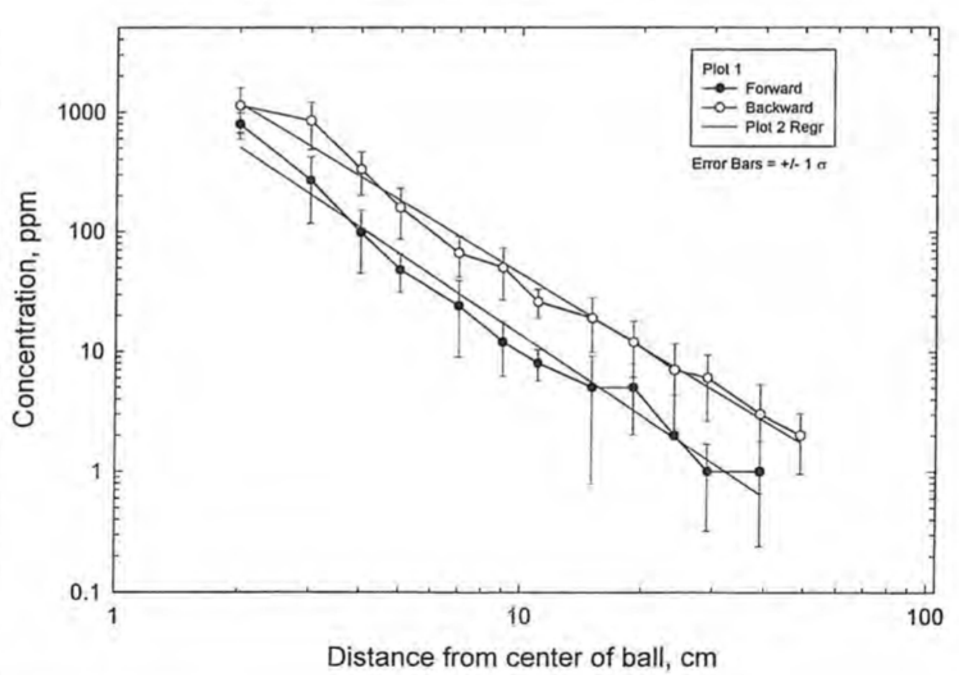


Figure 7b Combined Data 9/2 to 9/10/99



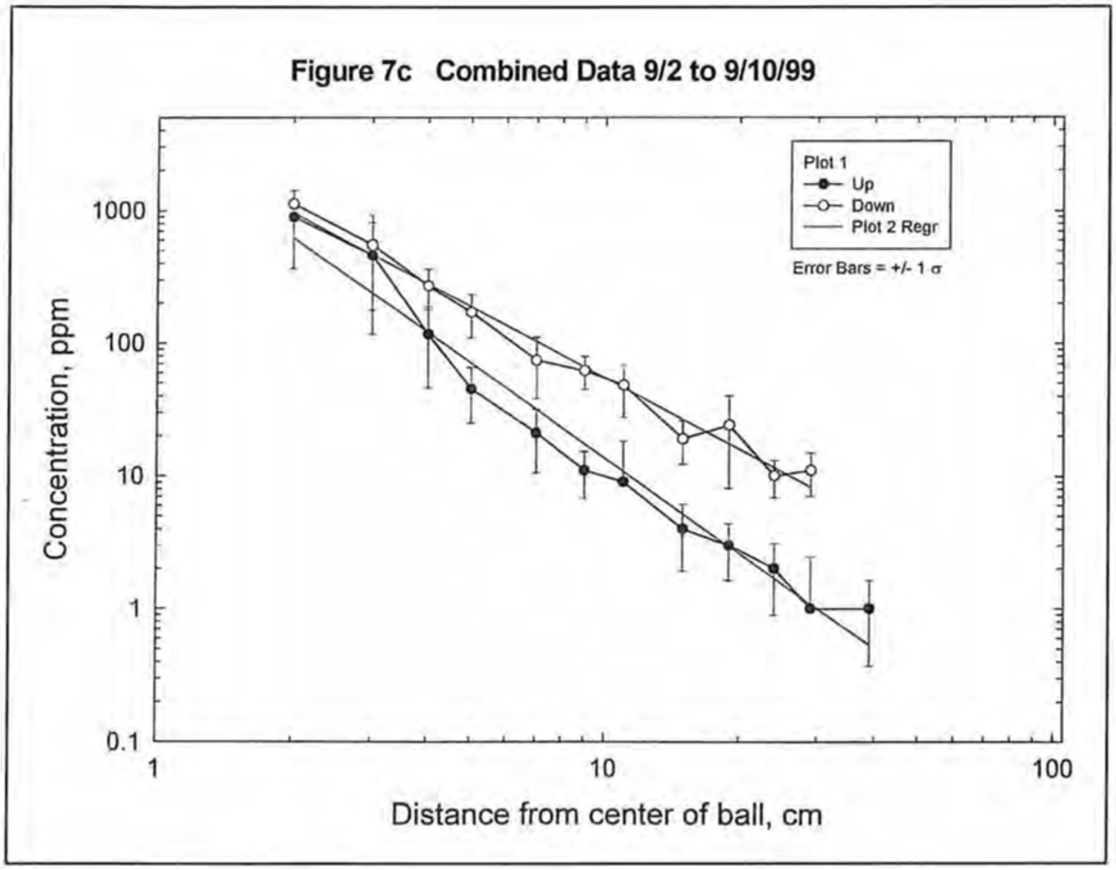
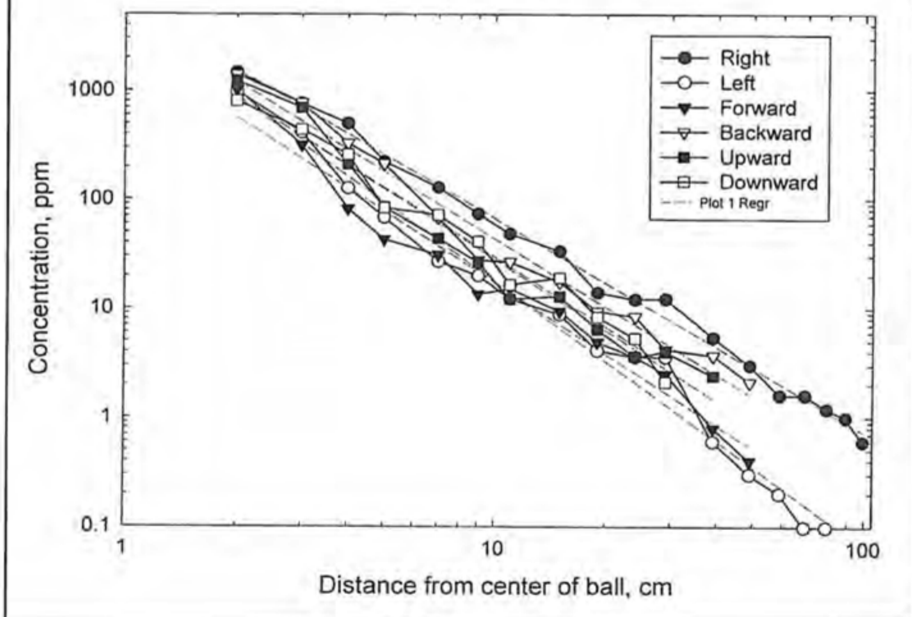


Figure 8 shows results for the six directions for the moderate activity condition. The pattern is similar, but the lines are closer together indicating better mixing and that there is less of an effect due to direction or reflection from surfaces. There is a bit more scatter for this condition because the data shown are based on only four replications instead of the seven replications for the stable condition. As with the stable condition, the right direction shows the slowest decay and the forward and upward directions show more rapid decay with distance. The slopes of the decay curves range from -1.96 to -2.43 with an average of -2.16 and a standard deviation of 0.17. Thus, the range of slopes is narrower and the slopes are slightly steeper; consistent with better mixing. There is a tenfold range in concentration at 0.5 meters for this stability condition.

Figure 8. Combined Data 9/15 to 9/24/99
Moderate Activity Mixing Condition



These results can be summarized in the form of a model to predict concentration within one meter from a point source in a laboratory environment. The straight lines shown in the figures 6 to 8 can be represented as power functions giving the decay of concentration with distance from a point source. Thus, for the stable condition, concentration at a distance x from a point source C(x) can be expressed by

$$C(x)=Ax^{b}=3{,}714x^{-2.02} \qquad (1)$$

where *x* is in centimeters. For x in meters Equation (1) becomes

$$C(x)=0.339x^{-2.02} \qquad (2)$$

For the moderate activity condition the single best equation is

$$C(x)=4{,}298x^{-2.16} \qquad (3)$$

for *x* in cm.

While the data shown here are limited, the following is our best estimate of the effect of the two factors that appear to influence the rate of decay. For the stable condition the exponent in equation 1, b = - 2.02 can be replaced by,

$$b=-1.89+d \qquad (4)$$

where:

d = - 0.42 if no reflecting surfaces are present in the direction of interest.

$d = +0.12$ if direction is in the prevailing air motion direction and a reflecting surface, such as a counter, is nearby in that direction.
$d = 0$ for all other conditions.

For the moderate activity condition the exponent becomes

$$b=-2.28+d \qquad (5)$$

where:

d = + 0.32 if the direction is in the prevailing wind direction and a reflecting surface, such as a lab bench, is nearby in that direction.
d = 0 for all other conditions.

Despite the limitations of these tests they do provide a detailed concentration decay model, not previously available, for concentration decay for distances of 0.01 to 1.0 m from a point source in a laboratory setting.

Recommendations:
The results outlined here are very promising, consequently we recommend that these ideas be developed further so that they can be put into practice. Specific needs are: (1) to evaluate concentration decay over a wider range of conditions so that the physical factor that affect decay rate can be identified; (2) to establish correlations between anemometry measured eddy diffusion coefficients and concentration decay rates; (3) to develop methods to predict decay rate and concentration at a location from anemometry data and source strength; and (4) to perform a field evaluation of these methods for well-defined single source exposure situations.

Conclusion:
There is very little published data on the transport of airborne contaminants within the indoor environment. The development of a near-field dispersion model to predict contaminant concentrations would provide an efficient screening tool for indoor work environments.

The use of the three-axis sonic anemometer is a promising technique in the development of a near-field dispersion model. The 3-axis anemometer data can be used in characterizing the turbulent mixing characteristics of indoor environments with varying levels of turbulent intensity. Through the use of computer data analysis programs, such as the serial correlation and defined angle range programs, this anemometer data can be used to estimate eddy diffusion coefficients. Eddy diffusion coefficients can then be coupled with mass-balance models to give more accurate predictions of contaminant concentrations within the near field (0 to 3 meters) of the indoor environment.

The data analysis programs previously described has proven successful at estimating eddy diffusion coefficients in a variety of turbulent conditions. The eddy diffusion coefficients calculated based on the anemometer data can be compared with those calculated by iteratively solving mass-balance concentration equations. Predicted concentration profiles obtained from mass-balance models can be compared against actual measured concentrations to determine which eddy diffusion coefficients provide the most accurate concentration estimates.

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3. Application of biologic monitoring and biomarkers of exposure for exposure assessment and hazard surveillance

To make use of biologic monitoring, biomarkers of exposure, and toxicokinetic modeling to better estimate internal and target tissue dose from exposure to single and multiple chemical agents and evaluate interactive effects associated with toxicokinetic interaction.

The published, accepted, or submitted papers or reports for this section are found in Appendix B. There are seven documents. The titles are as follows:

Toxicokinetic interaction of 2,5-hexanedione and methyl ethyl ketone, R.C. Yu, D. Hattis, and J.R. Froines, Submitted to Archives of Toxicology

Progress report: Metabolic interaction between styrene and butadiene, A. Cho, D. Schmitz and J.R. Froines

Short term non-invasive biomarkers for the processes of producing long term lung damage—evaluation of the feasibility of candidate measurement systems, S. Eylam, D. Hattis, and J. R. Froines.

Optimized portable cordless vacuum method for sampling dry, hard surfaces for dusts, S.Y. Kim, S. Que Hee, and J.Froines, Appl. Occup. Environ. Hyg., 15: 503-511.

Surface sampling for a pesticide in dust and small spills of a solid dye, S. Que Hee, Y. Shen, and J.C. Tso, Accepted, Appl. Occup. Environ. Hyg.

Effect of dust on the viability of Vibrio fischeri in the microtox test, Ecotoxicol. Environ. Safety, Submitted, Ecotox. Environ. Safety

Microtox test as a validation method for surface sampling of bacteria in dust, K. Park, Masters thesis, Department of Environmental Health Sciences, UCLA School of Public Health

Dr. John R. Froines and colleagues

Rong Chun Yu, Dale Hattis, Elliot M. Landaw, John R. Froines

Toxicokinetic Interaction of 2,5-Hexanedione and Methyl Ethyl Ketone

Abstract
Co-exposure to methyl ethyl ketone (MEK) potentiates the neurotoxicity of n-hexane in humans as well as in animals. This effect is associated with increased persistence of 2,5-hexanedione (2,5-HD) in blood, probably due to inhibition of 2,5-HD metabolism by MEK. There is no previous quantitative toxicokinetic model describing this interaction. In this study we constructed a toxicokinetic model to depict the inhibition of 2,5-HD metabolism by MEK. Experimental data of 2,5-HD blood concentrations in rats from a published study were used to estimate model parameters. Three different inhibition mechanisms: competitive, uncompetitive, and noncompetitive, were evaluated. Extrapolation from high to low doses was made to assess the effects of MEK on 2,5-HD metabolism beyond the experimental conditions. We found the developed model successfully described the toxicokinetic behavior of 2,5-HD that was inhibited by MEK. The competitive inhibition was regarded as the most probable mechanism ($V_{max,HD}$ = 7.6 mg/hr, K_m = 32.2 mg/L, and $K_{i,MEK}$ = 65.5 mg/L) to co-exposure to MEK. The biological half-life of 2,5-HD appeared to be a linear combination of the apparent Michaelis-Menten constant, 2,5-HD and MEK concentrations in the blood of rats. The AUC of 2,5-HD in rats was a nonlinear function of 2,5-HD and MEK concentrations in the blood. This study highlights the importance of the effect of metabolic deactivation of 2,5-HD by MEK, illustrating the advantage of toxicokinetic modeling to investigate chemical interactions associated with exposure to multiple chemical agents.

Keywords: chemical mixture, toxicokinetic interaction, competitive inhibition, 2,5-hexanedione, methyl ethyl ketone, biological half-life, AUC

Abbreviations: 2,5-HD: 2,5-hexanedione, MEK: methyl ethyl ketone, MnBK: methyl n-butyl ketone, AUC: area under the serum concentration-time curve

Symbols: V_{max}: rate of maximum reaction of Michaelis-Menten kinetics (mg/hr); K_m: apparent constant of Michaelis-Menten kinetics (mg/L); $V_{max,HD}$: rate of maximum reaction of 2,5-HD metabolism (mg/hr); $K_{m,HD}$: apparent Michaelis-Menten constant of 2,5-HD metabolism (mg/L); $V_{max,MEK}$: rate of maximum reaction of MEK metabolism (mg/hr); $K_{m,MEK}$: apparent constant of MEK metabolism (mg/L); $K_{i,MEK}$: constant of 2,5-HD inhibition by MEK (mg/L); $K_{i,HD}$: constant of MEK inhibition by 2,5-HD (mg/L); M_{HD}: mass of 2,5-HD in the blood (mg); M_{MEK}: mass of MEK in the blood (mg); C_{HD}: blood concentration of 2,5-HD (mg/L); $C_{HD}(0)$: initial blood concentration of 2,5-HD (mg/L) after administration of 2,5-HD; C_{MEK}: blood concentration of MEK (mg/L); V_{HD}: volume of distribution of 2,5-HD (L or mL), equivalent to blood; V_{MEK}:

volume of distribution of MEK (L or mL), equivalent to blood; BW^{rat}: body weight of rats (kg); BW^{human}: body weight of humans (kg); MW_{HD}: molecular weight of 2,5-HD (mg/mol)

Introduction

Humans are often exposed to multiple chemical agents in environmental and occupational settings. There is limited research on chemical interactions that result in enhancement or attenuation of toxicological outcomes. These interactions can be broadly divided into toxicokinetic or toxicodynamic phases. As seen in Figure 1 (*1-4*), toxicokinetic interactions may occur during the process of absorption, metabolic activation and deactivation, and elimination. Toxicodynamic interactions take place during cellular and molecular processes of binding to macromolecules or cellular membranes, repair and disassociation of macromolecular adducts, damage, and recovery or regeneration of target cells. The focus of this research was to investigate the toxicokinetic basis of metabolic interactions that were responsible for the enhancement of potential health effects due to co-exposure to 2,5-hexanedione (2,5-HD) and methyl ethyl ketone (MEK).

n-Hexane is known to cause neurotoxicity among occupationally exposed individuals and there are numerous reports of polyneuropathies associated with "glue sniffing" of hexane containing solvents and glues (*5-7*). The neurotoxic effect is characterized by loss of sensation and distal reflexes in the feet and hands after prolonged exposure to n-hexane. The current knowledge to explain this pathogenesis is formation of pyrrole from a hexane metabolite 2,5-HD, and subsequent reaction of the oxidized pyrrole with protein nucleophiles (*7*). In addition to central-peripheral distal axonopathy, experimental animals exposed to 2,5-HD exhibit testicular atrophy (*8,9*), possibly resulting from the apoptosis of the germ cells (*10,11*).

Metabolism of n-hexane involves complex pathways (Figure 2). n-Hexane is first metabolized by hepatic mixed-function oxidase system to form 2-hexanol. The latter is metabolized further to either methyl n-butyl ketone (MnBK) or 2,5-hexanediol and then to 5-hydroxy-2-hexanone. Oxidation of 5-hydroxy-2-hexanone leads to the formation of 2,5-HD (*12*). 2,5-HD may be excreted from urine in free form or undergoes further metabolism to produce 4,5-dihydroxy-2-hexanone that is excreted from urine as the glucuronide (*13*). 2,5-HD is considered the ultimate toxic metabolite and the neurotoxic potency of n-hexane is strongly correlated with the area under the serum concentration-time curve (AUC) of 2,5-HD, not the applied dose of n-hexane (*12,14*).

MEK is often used as a solvent in the manufacturing of colorless synthetic resins, artificial leather, rubbers, lacquers, varnishes, and glues. It is usually found in mixtures with other solvents, including n-hexane (*15*). Neurotoxicity increases as a result of co-exposure to MEK and either n-hexane, MnBK, or 2,5-HD in human studies, in vivo, and in vitro studies. The enhanced effects of MEK on n-hexane-induced neurotoxicity are unequivocal. MEK metabolism potentially interferes with n-hexane metabolism and has implications for toxicokinetic interaction. MEK is first metabolized to either 2-butanol, a minor process, or 3-hydroxy-2-butanone, a microsomal ω-1 oxidation and the limiting step of MEK metabolism. The latter metabolite is further metabolized to 2,3-butanediol (*16,17*). Because of similarities between the biotransformation of MEK and n-hexane it is plausible there may be competition between the two pathways.

Co-exposure to MEK may affect more than one step in the metabolism of n-hexane. Previous experiments suggest the concentration of 2,5-HD in blood decreases more slowly when rats are simultaneously exposed to MnBK and MEK (*18*), n-hexane and MEK (*19*), as well as 2,5-HD and MEK (*20*). AUC of 2,5-HD in blood increases in greater values in rats treated with 2,5-HD and MEK than those treated with 2,5-HD alone (*14*). The clearance of 2,5-HD in urine increases by 6-fold in animals co-administered both MnBK and MEK (*21*), but decreases in animals co-exposed to n-hexane and MEK (*22-24*). Krishnan and his colleagues (25) suggest hexane is an example of exposure to a single chemical that results in concomitant exposure to many chemicals because of the complex biotransformation processes. Co-exposure to MEK further complicates these interactions. Currently, there is no information in the literature describing these complex interactions. To investigate such complexity in a manageable manner it is necessary to seek simplifying assumptions to limit the study to a workable scope.

The objective of this study was to evaluate the efficacy of toxicokinetic modeling to investigate toxicological interaction between 2,5-HD and MEK. A toxicokinetic interaction model was developed and its kinetic parameters were estimated. The underlying toxicokinetic mechanisms of interaction: competitive, noncompetitive, or uncompetitive inhibition, were evaluated. The model was extrapolated from high to low doses to examine the effect of co-exposure to MEK on 2,5-HD AUC.

Materials and Methods

Materials

Published data of Yasui et al. (*20*) that investigates the blood concentration of 2,5-HD as influenced by co-exposure to 2,5-HD and MEK were selected to estimate model parameters. The authors subcutaneously injected 2.6 mmol/kg 2,5-HD alone or 2.6 mmol/kg 2,5-HD plus MEK at 2.6 mmol/kg and 13 mmol/kg to male Wistar rats. Following treatment for 0.5, 1, 2, 4, 8, and 16 hr, they sacrificed the animals and determined the blood concentrations of 2,5-HD.

A Model of Toxicokinetic Interaction between 2,5-HD and MEK

We addressed three issues on the toxicokinetic behavior of 2,5-HD as influenced by MEK: metabolism of 2,5-HD, metabolism of MEK, and the toxicokinetic interaction between 2,5-HD and MEK. A single saturable pathway was used to describe the deactivation and elimination of 2,5-HD in blood (Figure 3). 2,5-HD was assumed to be instantaneously available to the systemic circulation in rats administered 2,5-HD via subcutaneous injection. After the treatment, the mass balance governing 2,5-HD in the blood was

$$\frac{dM_{HD}}{dt} = -\frac{V_{max,HD} \cdot C_{HD}}{K_{m,HD} + C_{HD}}, \qquad (1)$$

where M_{HD} = mass of 2,5-HD in the blood (mg); $C_{HD} = M_{HD}/V_{HD}$, concentration of 2,5-HD in the blood (mg/L); V_{HD} = volume of distribution of 2,5-HD (L), equivalent to blood; $V_{max,HD}$ = maximum elimination rate of 2,5-HD (mg/hr); and $K_{m,HD}$ = apparent Michaelis constant for 2,5-HD metabolism (mg/L).

Similarly, a single compartment model was used to model the metabolism of MEK in blood (Figure 3), with parameters $V_{max,MEK}$ and $K_{m,MEK}$. Following the treatment of MEK, the mass balance governing MEK in the blood was

$$\frac{dM_{MEK}}{dt} = -\frac{V_{max,MEK} \cdot C_{MEK}}{K_{m,MEK} + C_{MEK}}, \tag{2}$$

where M_{MEK} = mass of MEK in the blood (mg); $C_{MEK} = M_{MEK}/V_{MEK}$, concentration of MEK in the blood (mg/L); V_{MEK} = volume of distribution of MEK (L), equivalent to blood; $V_{max,MEK}$ = maximum elimination rate of MEK (mg/hr); and $K_{m,MEK}$ = apparent Michaelis constant for MEK metabolism (mg/L).

Figure 3 depicts the toxicokinetic model of the interaction between 2,5-HD and MEK. The interaction may occur by one of three inhibition modes: competitive, uncompetitive, or noncompetitive. Competitive inhibition occurs when an inhibitor competes directly with a normal substrate for the same binding sites available on the enzyme. If MEK competitively inhibits 2,5-HD metabolism, Equation (1) can be modified (*26*), as follows,

$$\frac{dM_{HD}}{dt} = -\frac{V_{max,HD} \cdot C_{HD}}{K_{m,HD} \cdot \left[1 + C_{MEK}/K_{i,MEK}\right] + C_{HD}}, \tag{3}$$

where $K_{i,MEK}$ (mg/L) in Equation (3) refers to the constant for competitive inhibition of 2,5-HD metabolism by MEK.

Uncompetitive inhibition results from an inhibitor binding to the enzyme-substrate complex to produce an inactive enzyme-substrate-inhibitor complex. The presence of the inhibitor molecule not only affects formation of the final product but also influences production of the enzyme-substrate complex. If the interaction of 2,5-HD and MEK occurred under this mechanism, Equation (1) can be modified (*26*), as follows

$$\frac{dM_{HD}}{dt} = -\frac{C_{HD} \cdot \left[\dfrac{V_{max,HD}}{1 + C_{MEK}/K_{i,MEK}}\right]}{C_{HD} + \left[\dfrac{K_{m,HD}}{1 + C_{MEK}/K_{i,MEK}}\right]}, \tag{4}$$

where $K_{i,MEK}$ (mg/L) in Equation (4) refers to the constant for uncompetitive inhibition of 2,5-HD metabolism by MEK.

In noncompetitive inhibition, an inhibitor binds not only to the free enzyme to form an enzyme-inhibitor complex but also to the enzyme-substrate complex to generate an inactive enzyme-substrate-inhibitor complex. If the interaction of 2,5-HD and MEK operated in this mode, Equation (1) can be modified (*26*), as follows

$$\frac{dM_{HD}}{dt} = -\frac{C_{HD} \cdot \left[\dfrac{V_{max,HD}}{1 + C_{MEK}/K_{i,MEK}} \right]}{K_{m,HD} + C_{HD}}, \tag{5}$$

where $K_{i,MEK}$ (mg/L) in Equation (5) refers to the constant for noncompetitive inhibition of 2,5-HD metabolism by MEK.

Influence of Metabolic Inhibition on Biological Half-Life of Chemical Mixtures

The biological half-life of 2,5-HD ($T_{½,HD}$) as inhibited by MEK, by definition (*27*), can be described as:

$$T_{½,HD} = \frac{0.693 \cdot V_{HD}}{\dfrac{dM_{HD}}{dt} / C_{HD}}, \tag{6}$$

where V_{HD}, is volume distribution of 2,5-HD and the denominator $\left(\frac{dM_{HD}}{dt} / C_{HD} \right)$ is the clearance (*27*) of 2,5-HD. In the case of MEK competitively inhibiting 2,5-HD metabolism, substitution of Equation (3), without the negative sign for elimination, into Equation (6) and rearrangement of the latter equation give

$$T_{½,HD} = \frac{0.693 \cdot V_{HD}}{V_{max,HD}} (K_{m,HD} + C_{HD} + \frac{K_{m,HD}}{K_{i,MEK}} \cdot C_{MEK}). \tag{7}$$

In the cases of MEK uncompetitively and noncompetitively inhibiting 2,5-HD metabolism, the $T_{½,HD}$ can be written in Equations (8) and (9), respectively, as follows:

$$T_{½,HD} = \frac{0.693 \cdot V_{HD}}{V_{max,HD}} (K_{m,HD} + C_{HD} + \frac{C_{HD}}{K_{i,MEK}} \cdot C_{MEK}), \tag{8}$$

and

$$T_{½,HD} = \frac{0.693 \cdot V_{HD}}{V_{max,HD}} (K_{m,HD} + C_{HD} + \frac{K_{m,HD} + C_{HD}}{K_{i,MEK}} \cdot C_{MEK}). \tag{9}$$

Estimation of Model Parameters

Liira et al. (*28*) report the values of $V_{max,MEK}$ and $K_{m,MEK}$ for humans, 30 μmol/min (=130 mg/hr) and 2 μM (=0.14 mg/L), respectively. In this study, we assumed the value of $K_{m,MEK}$ of rats was the same as that in Liira's study, i.e., 0.14 mg/L. Based on the principle described by Gargas et al. (*29*), the value of $V_{max,MEK}$ was extrapolated from humans to rats, as follows

$$V_{max,MEK}^{rat} = V_{max,MEK}^{human} \times \left(\frac{BW^{rat}}{BW^{human}} \right)^{0.7} = 130\ mg/hr \times \left(\frac{0.272\ kg}{71\ kg} \right)^{0.7} = 2.64\ mg/hr,$$

where body weight (BW) of rats and humans were based on data reported by Yasui et al. (*20*) and Liira et al. (*28*), respectively. Table 1 shows the equivalent volume of distribution of MEK to blood (V_{MEK} = 280 ml, blood equivalent), which was estimated by physical volume of the major physiological compartments (including fat, liver, slow-perfusion tissue group, rich-perfusion tissue group, and liver) of rats and the tissue/blood partition coefficients of MEK in these compartments.

The AR program in BMDP (30) was used to fit experimental data and estimate kinetic parameters. The program is a derivative-free nonlinear regression procedure that estimates the parameters for a wide variety of nonlinear functions by the method of least squares (or equivalent to the method of maximum likelihood) using a pseudo-Gauss-Newton iterative algorithm. It simultaneously estimated 4 unknown model parameters: $V_{max,HD}$, $K_{m,HD}$, V_{HD}, and $K_{i,MEK}$, where V_{HD} was calculated as follows:

$$V_{HD} = \frac{BW^{rat} \times Dose \times MW_{HD}}{C_{HD}(0)} \times 1000, \quad (10)$$

In Equation (10), BW^{rat} = 0.272 kg (*20*), Dose = 2.6 mmol/kg (*20*), MW_{HD} = 114 mg/mmol, and $C_{HD}(0)$, the initial blood concentration of 2,5-HD (mg/L). The AR program run three separate models that assumed the toxicokinetic interaction between 2,5-HD and MEK were competitive, un-competitive, and non-competitive inhibition, respectively. It reported the estimates and asymptotic standard errors of kinetic parameters.

Model Simulations

Simulation studies were carried out to extrapolate the effect of co-exposure to MEK on the AUC of 2,5-HD from high to low doses. We run a total of 186 simulations, including any combinations of six 2,5-HD regimens (0.1, 0.3, 0.6, 1.2, 2.0 and 3.0 mmol/kg) and thirty-one MEK regimens (0 to 3.0 mmol/kg, with an increment of 0.1 mmol/kg). In each simulation experiment, the AUC of 2,5-HD was estimated by the trapezoidal rule, an approximate numeric integration algorithm (*27*).

Results

The developed model, which assumed MEK competitively inhibited 2,5-HD metabolism, successfully fit the experimental data of Yasui et al. (*20*) (Figure 4). The estimates of the kinetic parameters were $V_{max,HD}$ = 7.6 mg/hr, $K_{m,HD}$ = 32.2 mg/L, V_{HD} = 264 mL, and $K_{i,MEK}$ = 65.5 mg/L. It not only predicted the behavior of 2,5-HD in the blood of the rats exposed to 2.6 mmol/kg 2,5-HD alone (the line labeled with "HD" in Figure 4) reasonably well but also those exposed to 2.6 mmol/kg 2,5-HD plus 2.6 mmol/kg MEK (the line labeled with "HD+MEK") and 2.6 mmol/kg 2,5-HD plus 13 mmol/kg MEK (the line labeled with "HD+5MEK"). This toxicokinetic model showed the persistence of 2,5-HD in rats was MEK dependent; the higher MEK dose the more profound the persistence of 2,5-HD.

Figures 5 and 6 show the uncompetitive and noncompetitive inhibition models also fit reasonably well to the experimental data. The goodness-of-fit was not substantially different from that of the competitive model (Figure 4). In comparison with the kinetic parameters, the values of V_{HD}, $V_{max,HD}$, and $K_{m,HD}$ were not substantially different (Table 2). The mean squared error (MSE) obtained from the competitive model (MSE=0.008124) was smaller than, but not substantially different from, those of the uncompetitive (MSE=0.008747) and noncompetitive (MSE=0.008424) models. The inhibition constant for competitive inhibition model ($K_{i,MEK}$ = 65.5 ±8.5 mg/L) was significantly lower than those of noncompetitive inhibition (403±86.5 mg/L) and uncompetitive inhibition (440±77.1 mg/L).

The developed toxicokinetic model was used to extrapolate the behavior of 2,5-HD in rats as influenced by MEK from high to low doses. Figure 7 depicts the AUC of 2,5-HD as a function of the co-exposed dose of MEK when rats are co-administered 2,5-HD at 0.1, 0.3, 0.6, 1.2, 2.0, and 3.0 mmol/kg. The figure shows the $\log_{10}$(AUC) approximately linearly increases with increase in MEK dose ranging from 0 to 3 mmol/kg. This corresponds to an increase in AUC by a factor of approximate 10^{β} per unit dose of MEK, where β is the slope of the linear relationship.

Table 3 summarizes the slopes of the linear relationships and the corresponding values of 10^{β} at various doses of 2,5-HD. The slopes decreased from 0.399 to 0.09 [$\log_{10}$(AUC) per mmol/kg MEK] with increase in 2,5-HD doses from 0.1 to 3.0 mmol/kg. For every increment of 1 mmol/kg MEK, the AUC approximately increases 2.5 fold in the rat co-administered 0.1 mmol/kg 2,5-HD. In comparison, the AUC approximately increases only 1.23 fold at 3.0 mmol/kg 2,5-HD (Table 3).

Equations (7)-(9) show $T_{½,HD}$ is a linear combination of $K_{m,HD}$, C_{HD} and C_{MEK}. Figure 8 depicts the $T_{½,HD}$ as a function of blood MEK concentration at various blood concentrations of 2,5-HD at 10, 75, 150, 250 and 350 mg/L. At 10 mg/L 2,5-HD, approximately equal to the initial 2,5-HD concentration of the rats subcutaneously injected with 0.1 mmol/kg, the $T_{½,HD}$ was 1 hr when there was no inhibition by MEK. In comparison, at 350 mg/L, approximately equal to the initial 2,5-HD concentration of the rats exposed to 3 mmol/kg, the half-life was 9.2 hr. When rats were co-administered with MEK, $T_{½,HD}$ increased 1.18 hr for every increment of 100 mg/L blood concentration of MEK.

Discussion

The objective of this study was to use toxicokinetic modeling to investigate the mechanistic basis for the interaction of MEK with 2,5-HD. The model focused upon the metabolism and elimination of 2,5-HD, without considering the complex interactions of intermediary metabolites (Figures 1 and 2). The agreement between model predictions and experimental data suggested reasonable model specification and parameter estimation, as well as the probable mechanism of metabolic inhibition between 2,5-HD and MEK. The model, although not physiologically based, captured the essential feature of 2,5-HD metabolism and its interaction with MEK and demonstrated the utility of toxicokinetic modeling in investigating metabolic interactions between chemical mixtures. It highlighted the significance of inhibiting deactivation of a toxic metabolite on its persistence in the body.

Metabolic inhibition was the mechanism likely responsible for increased persistence of 2,5-HD in rats co-exposed to 2,5-HD and MEK. Ralston et al. (*14*) found concomitant administration of MEK reduced blood 2,5-HD clearance and increased the AUC of 2,5-HD. Yasui et al. (*20*) demonstrated that blood 2,5-HD concentration in rats increased significantly in the co-exposure groups and that the increase was MEK dose-dependent. These experiments unequivocally demonstrated that increased persistence of 2,5-HD was due to MEK. However, the kinetic mechanism had not been elucidated by these two studies. We employed a toxicokinetic model to test the hypothesis that inhibition of metabolism was the likely mechanism for the increased persistence of 2,5-HD in animals co-exposed to 2,5-HD and MEK. Our results suggest a single Michaelis-Menten kinetic pathway of the elimination satisfactorily describes 2,5-HD metabolism in the rat.

The method of goodness-of-fit did not clearly identify the mode of metabolic inhibition in this study although it has been used in other studies to elucidate the inhibitory mechanism of metabolic interactions between chemicals (*37,43-47*). In most cases, there is clear evidence that a particular inhibition mechanism provides better goodness-of-fit than the others in toxicokinetic modeling. However, as shown in Figures 4-6, it was difficult to discern which inhibition mechanism provided the best fit by comparing the goodness-of-fit in the figures. The mean squared error for the competitive inhibition model was slightly smaller than those for the uncompetitive and the noncompetitive models (Table 2). But, the differences could not be statistically tested because these three models were not nested. These results suggest that the goodness-of-fit of toxicokinetic modeling to experimental data may not always result in clearly differentiating mechanisms of inhibition mechanism in metabolic interaction studies.

In the case of 2,5-HD inhibition by MEK, the competitive mode might have operated more efficiently than uncompetitive and noncompetitive modes. From the perspective of toxicokinetic modeling, the major difference among these three inhibition modes was the inhibition constant $K_{i,MEK}$ (Table 2). Fitting the experimental data of Yasui et al. (*20*) to the competitive mode gave the smallest estimate of the inhibition constant (65.5 mg/L), compared to those of the uncompetitive (403 mg/L) and the noncompetitive modes (440 mg/L). These results were consistent with those found in the study of Thrall et al. (*45*), in which the inhibition constants of toluene and trichloroethylene in the competitive mode were reported to be smaller than those of the uncompetitive and noncompetitive modes. The authors argued that competitive inhibition was the most plausible type of metabolic interaction between these two solvents because the inhibition constants are closest to the corresponding Michaelis-Menten constants. We considered competitive inhibition to be operating more efficiently than uncompetitive and noncompetitive modes because of a much lower inhibition constant for competitive inhibition.

Extrapolation of the behavior of 2,5-HD AUC in the blood from high to low doses of 2,5-HD and MEK was the major application for the toxicokinetic model developed in this study. The experimental data of Yasui et al. (*20*) focused on the behavior of 2,5-HD as influenced by MEK in high dose scenarios. The concave nature the of 2,5-HD concentration profiles highlights the saturation of 2,5-HD metabolism (HD lines in Figures 4-6) and increased persistence of 2,5-HD by co-administration of MEK (HD+MEK and HD+5MEK lines). Since 2,5-HD AUC has been shown to correlate with the neurotoxic potency of n-hexane (*12,14*), it was extrapolated from high doses, more often used in toxicological experiments, to low dose regions, relevant at the exposure levels found in the environment or even the workplace. Figure 7 depicts the predicted 2,5-HD AUC in rats subcutaneously co-administered with 2,5-HD and MEK at a variety of dose ranges. Although our study applied toxicokinetic modeling to shed new light upon the impact of MEK on 2,5-HD metabolism, we did not take into consideration of species extrapolation (rats to humans), route differences (subcutaneous injection to inhalation), and exposure regimen (acute to chronic) for the developed toxicokinetic model. Further studies are needed to address these issues.

The 2,5-HD $T_{½}$ is quantitatively related to the kinetic parameters of metabolic inhibition. Yasui et al. (*20*) showed MEK is capable of prolonging the 2,5-HD $T_{½}$ in the blood, which was thought to relate to the potentiation of 2,5-HD neurotoxicity by MEK. Zhao et al. (50) showed MEK (as well as acetone and toluene) decreased the elimination rate constants of 2,5-HD (or equivalent to prolong 2,5-HD $T_{½}$) in co-administration groups. These empirical observations consistently suggest a qualitative relationship between 2,5-HD $T_{½}$ and the concentrations of 2,5-HD and MEK. However, there have been no quantitative relationships documented in the literature. In this study, we showed that 2,5-HD $T_{½}$ following co-administration of 2,5-HD and MEK was a linear combination of the apparent Michaelis-Menten constant, the blood concentrations of 2,5-HD and MEK, and depended on the nature of the metabolic inhibition [Equations (7)-(9)]. The limiting conditions of these relationships are discussed below:

1. At low concentrations of 2,5-HD ($C_{HD} \rightarrow 0$) and no MEK inhibition ($C_{MEK} = 0$), $T_{½,HD}$ in Equations (7)-(9) is reduced to a constant

$$T_{\frac{1}{2},HD} = \frac{0.693 \cdot V_{HD} \cdot K_{m,HD}}{V_{max,HD}},$$

a limiting condition of linear kinetics of metabolism.

2. When C_{HD} concentrations are relatively high and no MEK inhibition occurs ($C_{MEK} = 0$). Equations (7)-(9) can be reduced to

$$T_{\frac{1}{2},HD} = \frac{0.693 \cdot V_{HD}}{V_{max,HD}}(K_{m,HD} + C_{HD}),$$

a nonlinear kinetic condition of 2,5-HD metabolism that is consistent with the derivation by Gibaldi and Perrier (*27*).

3. When the blood concentration of MEK is high $T_{½,HD}$ is also a function of the MEK concentration that is multiplied by a factor $\left(\frac{K_{m,HD}}{K_{i,MEK}}\right)$, $\left(\frac{C_{HD}}{K_{i,MEK}}\right)$, or $\left(\frac{K_{m,HD} + C_{HD}}{K_{i,MEK}}\right)$ for

competitive, uncompetitive, or noncompetitive inhibition, respectively. These factors suggest that competitive inhibition operates more effectively in prolonging $T_{½,HD}$ than uncompetitive and noncompetitive inhibition modes because the inhibition constant of former mode is 6 fold lower (Table 2).

Although 2,5-HD and MEK can theoretically interact with each other (Figure 3), inhibition of MEK metabolism by 2,5-HD is relatively unimportant. We conducted a sensitivity analysis to examine the impact of the competitive inhibition constant of MEK by 2,5-HD ($K_{i,HD}$) on other kinetic parameters and mean squared errors. Our analyses found the models including $K_{i,HD}$ above 600 mg/L did not improve the goodness-of-fit at all, in comparison to the model including $K_{i,HD}$ at 600 mg/L. Under the latter condition, other kinetic constants were estimated to be: V_{HD} = 264.5 mL, $V_{max,HD}$ = 7.6 mg/hr, $K_{m,HD}$ = 32.2 mg/L, and $K_{i,MEK}$ = 66.0 mg/L. These values were very close to those estimated when $K_{i,HD}$ was not included in the model (V_{HD} = 264.3 mL, $V_{max,HD}$ = 7.6 mg/hr, $K_{m,HD}$ = 32.2 mg/L, and $K_{i,MEK}$ = 65.5 mg/L, see Table 2). The mean squared errors between these two conditions differed by only 1.5%. In contrast, when $K_{i,HD}$ was less than 600 mg/L, the kinetic parameters gradually departed from the values shown in Table 2. The mean squared errors also increased substantially, suggesting poor goodness-of-fit under the conditions of $K_{i,HD} < 600$ mg/L. Because the $K_{i,HD}$ did not improve the fit, we eventually eliminated $K_{i,HD}$ from the model to make it simpler without loss of descriptive power.

Metabolic interactions occurring in the process of n-hexane activation to 2,5-HD could affect the metabolism of n-hexane in the body. Andersen and Clewell (*31*) considered multiple competitive interactions between hexane, MnBK and 2,5-HD. They used PBPK modeling to describe the kinetics of the three compounds and suggested at high concentrations or continuous exposure the formation of 2,5-HD may be inhibited in part because 2,5-HD and MnBK might inhibit hexane metabolism. In a study of Iwata et al. (*23*), rats inhaled n-hexane plus MEK at 1000 ppm for 8 hrs. Forty-eight hour urinary excretion of 2-hexanol decreased in the animals exposed to n-hexane and MEK, suggesting production of 2-hexanol was inhibited by MEK. In another study (*24*), rats were exposed to hexane and MEK at 500 ppm 8 hrs a day for 33 weeks. The authors demonstrated a similar decrease in 2-hexanol elimination. The studies of Shibata et al. (*22,32*) showed that 2-hexanol level in serum and its elimination in urine decreased in animals exposed to mixture of hexane and MEK, compared to those exposed to hexane only. In a study of human volunteers exposed to a mixture of hexane and MEK (*33*), the serum concentration of 2,5-HD decreased and the time to reach maximum concentration of 2,5-HD increased. Previous studies show hydroxylation of hexane is inhibited by the presence of MEK as a result of competition for the CYP2E1 enzyme that is required for biotransformation of hexane (*34*) and MEK (*35,36*). In brief, many steps in the activation of n-hexane to 2,5-HD, as outlined in Figure 2, can be affected by co-exposure to MEK. Our study could not address this issue.

There is no compelling evidence to indicate that MEK affects the toxicity of hexane or MnBK at the toxicodynamic level. In one relevant report (*14*), rats were treated with 2.2 mmol/kg/day 2,5-[^{14}C]HD alone and in combination with 2.2 mmol/kg/day MEK for 3 weeks. Total ^{14}C activity was examined in peripheral nerve crude homogenate, neurofilament-enriched fraction of peripheral nerve, spinal cord crude homogenate, and neurofilment-enriched fraction of spinal cord. The binding of radiolabeled 2,5-HD to the nervous tissues and their corresponding neurofilament-enriched fractions in rats exposed to 2,5-HD plus MEK were not consistently different from that in animals exposed to 2,5-HD alone. These results indicate that enhancement of n-hexane-induced neurotoxicity by MEK does not result from increased binding of 2,5-HD to neurofilament at toxicodynamic level.

We conclude that the persistence of 2,5-HD in the blood of experimental animals probably results from competitive inhibition of 2,5-HD metabolism by MEK. The estimated values of kinetic parameters provide a quantitative basis for description of 2,5-HD deactivation metabolic process in the presence of MEK. The biological half-life of 2,5-HD appears to be a linear combination of the apparent Michaelis-Menten constant, 2,5-HD and MEK concentrations in the blood of rats. The AUC of 2,5-HD in rats is a nonlinear function of 2,5-HD and MEK concentrations in the blood. This study demonstrates the utility of toxicokinetic modeling in the investigation of metabolic interactions between chemical mixtures.

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Table 1. Estimation of Distribution Volume of MEK

Compartment	Volume[a], ml	Tissue/Blood[b]	Volume, ml (blood equiv.)
Fat	19.0	0.88	17
Liver	10.9	0.98	11
SPG	204.0	1.16	237
RPG	13.6	1.12[c]	15
Total			280

[a]Fat, liver, SPG (slow-perfusion tissue group), and RPG (rich-perfusion tissue group) consist of 4, 7, 5, and 75% of tissue volume, respectively (*41*).
[b]Tissue/blood partition coefficients were estimated by Perbellini et al. (*42*) for humans.
[c]This value was an average of tissue/blood partition coefficients of kidney, brain, and heart reported by Perbellini et al. (*42*).

Table 2. Parameters used to Fit Models of Different Inhibition Mechanisms

	Mode of Inhibition		
	Competitive	Uncompetitive	Noncompetitive
V_{HD} (mL)	264.3 ± 6.9[a]	275 ± 7.0	273.9 ± 6.9
$V_{max,HD}$ (mg/hr)	7.6 ± 0.7	6.7 ± 0.6	6.9 ± 0.6
$K_{m,HD}$ (mg/L)	32.2 ± 8.7	20.7 ± 7.0	22.8 ± 7.7
$K_{i,MEK}$ (mg/L)	65.5 ± 8.5	403.0 ± 86.5	440.2 ± 77.1
Mean Squared Error	0.008124	0.008747	0.008428

[a] Mean ± (asymptotic) standard errors.

Table 3. The Slope (β) of the Linear Relationship between $\log_{10}$(AUC) and MEK and 10^{β} at various Doses of 2,5-HD

2,5-HD Dose (mmol/kg)	β [$\log_{10}$(AUC) per MEK dose]	10^{β}
0.1	0.399	2.50
0.3	0.340	2.19
0.6	0.278	1.90
1.2	0.198	1.58
2.0	0.136	1.37
3.0	0.090	1.23

Captions of Figures

Figure 1. Paradigm of potential toxicological interactions of chemical mixtures [adapted from (*1*)-(*4*)].

Figure 2. Metabolism of n-hexane and its metabolites [adapted from (*12*) and (*13*)].

Figure 3. A diagram presentation of a metabolic interaction model of 2,5-HD and MEK. The big compartment represents the overall model that consists of two distinct compound-specific compartments: 2,5-HD and MEK. Elimination of the compound is characterized by Michaelis-Menten kinetic parameters $V_{max,HD}$ and $K_{m,HD}$ for 2,5-HD, and $V_{max,MEK}$ and $K_{m,MEK}$ for MEK. The inhibition of 2,5-HD by MEK ($K_{i,MEK}$) and that of MEK by 2,5-HD ($K_{i,HD}$) were employed to capture mutual inhibition between the two compounds.

Figure 4. Time course of 2,5-HD concentration in the serum of male Wistar rats subcutaneously injected with 2.6 mmol/kg 2,5-HD (HD), 2.6 mmol/kg 2,5-HD plus 2.6 mmol/kg MEK (HD+MEK) and 13 mmol/kg MEK (HD+5MEK). The solid lines are predictions of the competitive inhibition model (see Equation (3) for model specification and Table 2 for model parameters). The symbols represent experimental data from Yasui et al. (*20*).

Figure 5. Time course of 2,5-HD concentration in the serum of male Wistar rats subcutaneously injected with 2.6 mmol/kg 2,5-HD (HD), 2.6 mmol/kg 2,5-HD plus 2.6 mmol/kg MEK (HD+MEK) and 13 mmol/kg MEK (HD+5MEK). The solid lines are predictions of the uncompetitive inhibition model (see Equation (4) for model specification and Table 2 for model parameters). The symbols represent experimental data from Yasui et al. (*20*).

Figure 6. Time course of 2,5-HD concentration in the serum of male Wistar rats subcutaneously injected with 2.6 mmol/kg 2,5-HD (HD), 2.6 mmol/kg 2,5-HD plus 2.6 mmol/kg MEK (HD+MEK) and 13 mmol/kg MEK (HD+5MEK). The solid lines are predictions of the noncompetitive model (see Equation (5) for model specification and Table 2 for model parameters). The symbols represent experimental data from Yasui et al. (*20*).

Figure 7. Effects of co-exposure to MEK on 2,5-HD AUC at various doses of 2,5-HD. The competitive inhibition model (see Equation (3) for model specification and Table 2 for model parameters) predicts the values of 2,5-HD AUC, based on the assumption that rats were subcutaneously administered with 2,5-HD and MEK.

Figure 8. Effects of co-exposure to MEK on the biological half-life of 2,5-HD at various blood concentrations of 2,5-HD. The latter is a linear combination [see Equations (7)] of apparent Michaelis-Menten constant, the concentrations of 2,5-HD and MEK in blood.

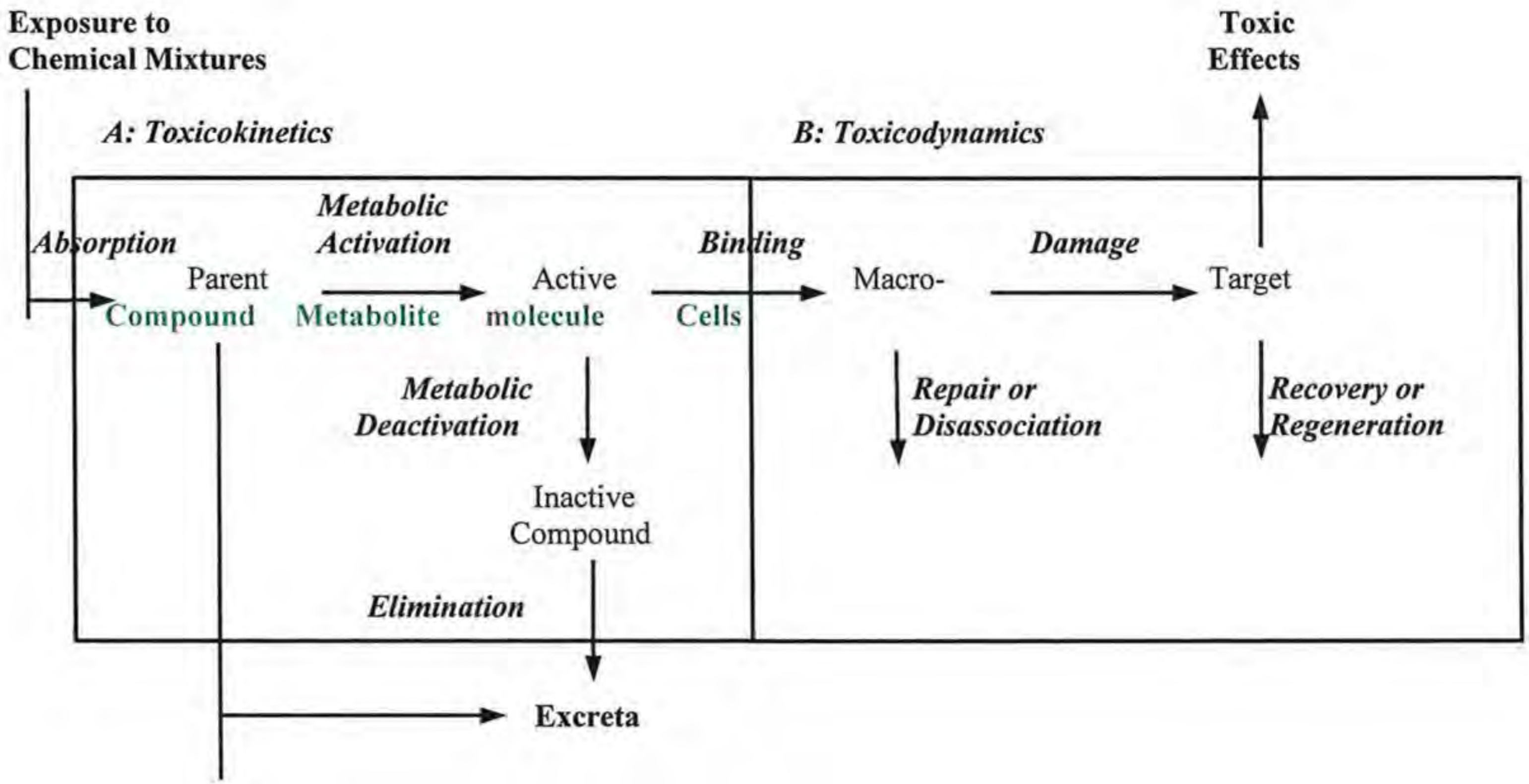

Exposure to Chemical Mixtures
Toxic Effects
A: Toxicokinetics
B: Toxicodynamics
Absorption
Parent Compound
Metabolic Activation
Active Metabolite
Binding
Macro-molecule
Damage
Target Cells
Metabolic Deactivation
Inactive Compound
Repair or Disassociation
Recovery or Regeneration
Elimination
Excreta

Figure 1

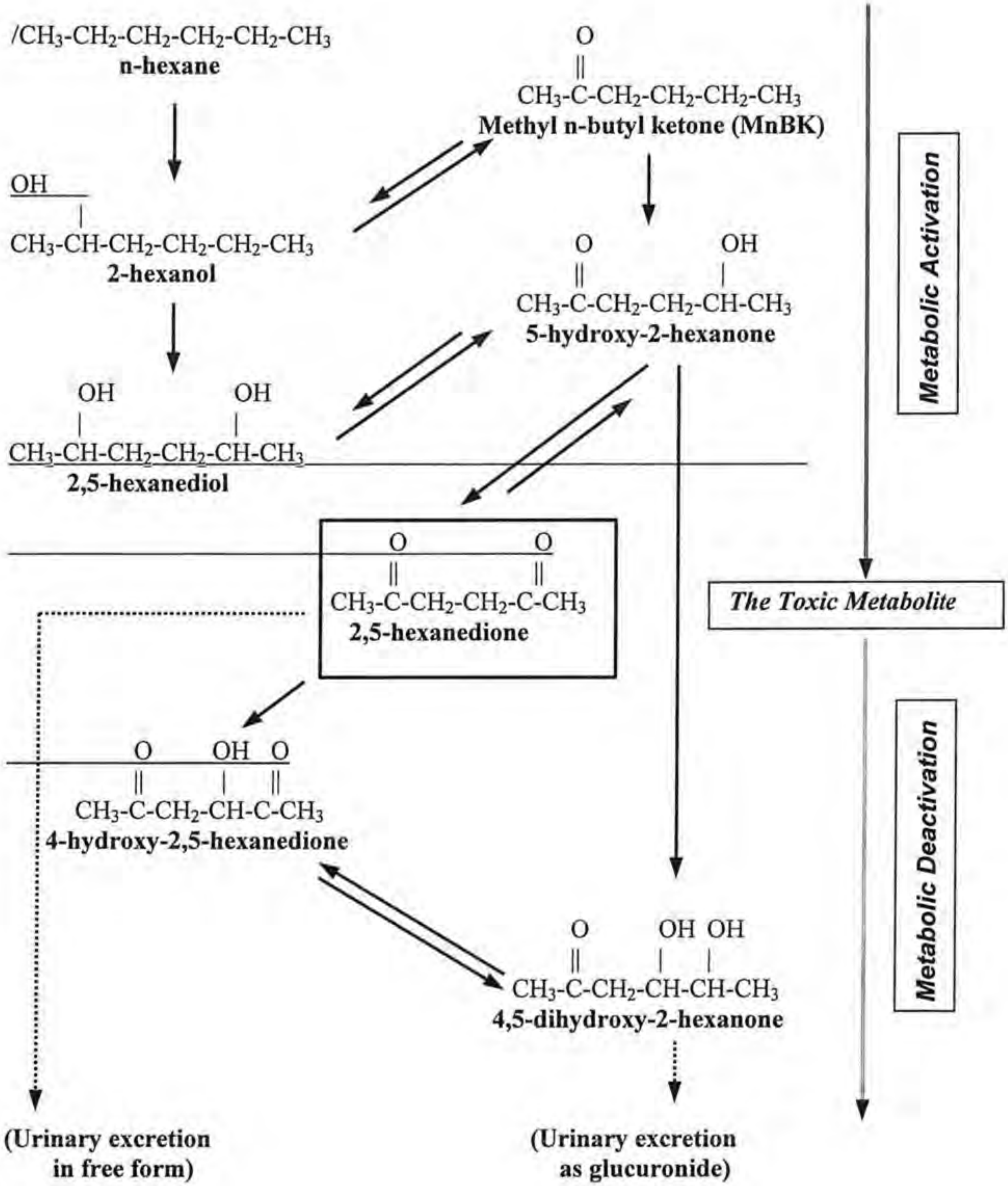

/CH3-CH2-CH2-CH2-CH2-CH3
n-hexane
Methyl n-butyl ketone (MnBK)
2-hexanol
5-hydroxy-2-hexanone
2,5-hexanediol
2,5-hexanedione
The Toxic Metabolite
Metabolic Activation
Metabolic Deactivation
4-hydroxy-2,5-hexanedione
4,5-dihydroxy-2-hexanone
(Urinary excretion
in free form)
(Urinary excretion
as glucuronide)

Figure 2

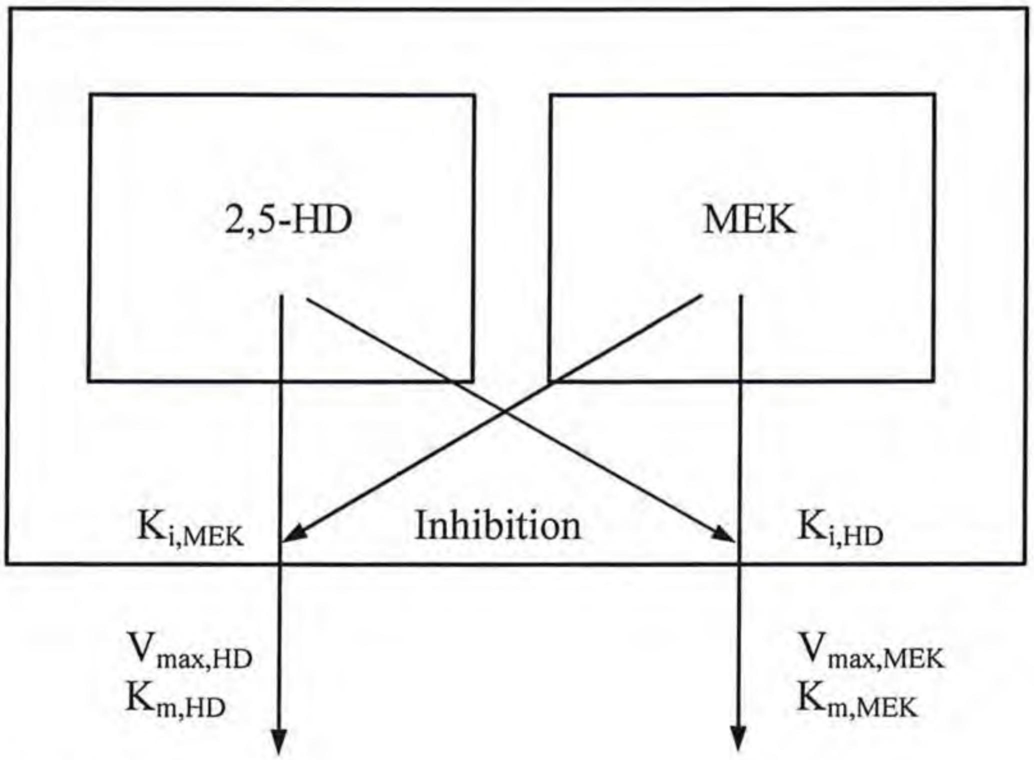


Figure 3

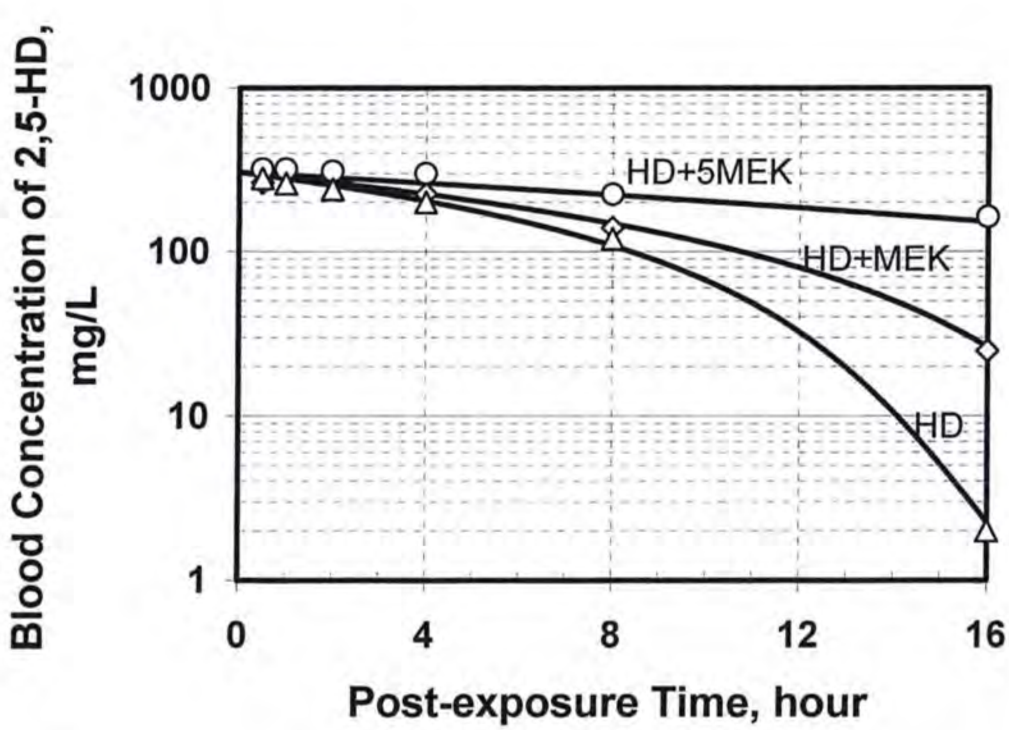


Figure 4

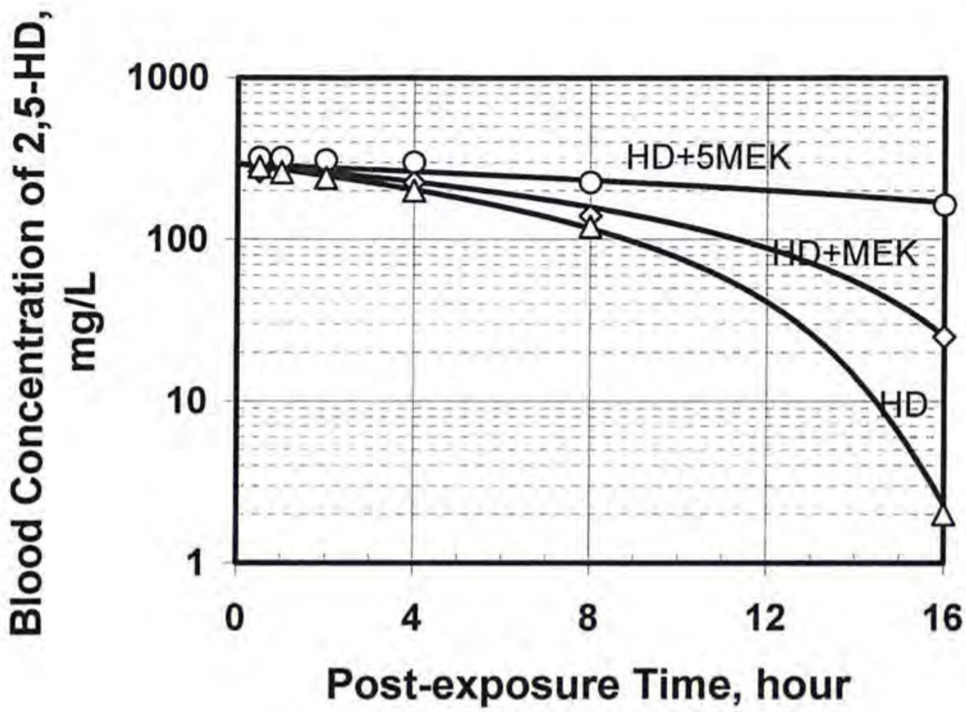


Figure 5

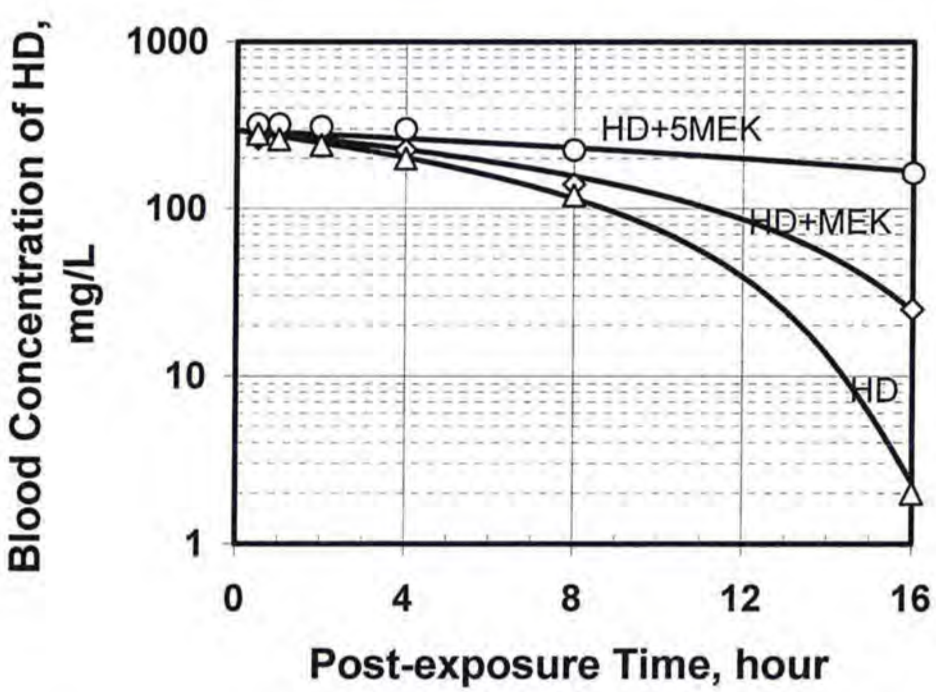


Figure 6

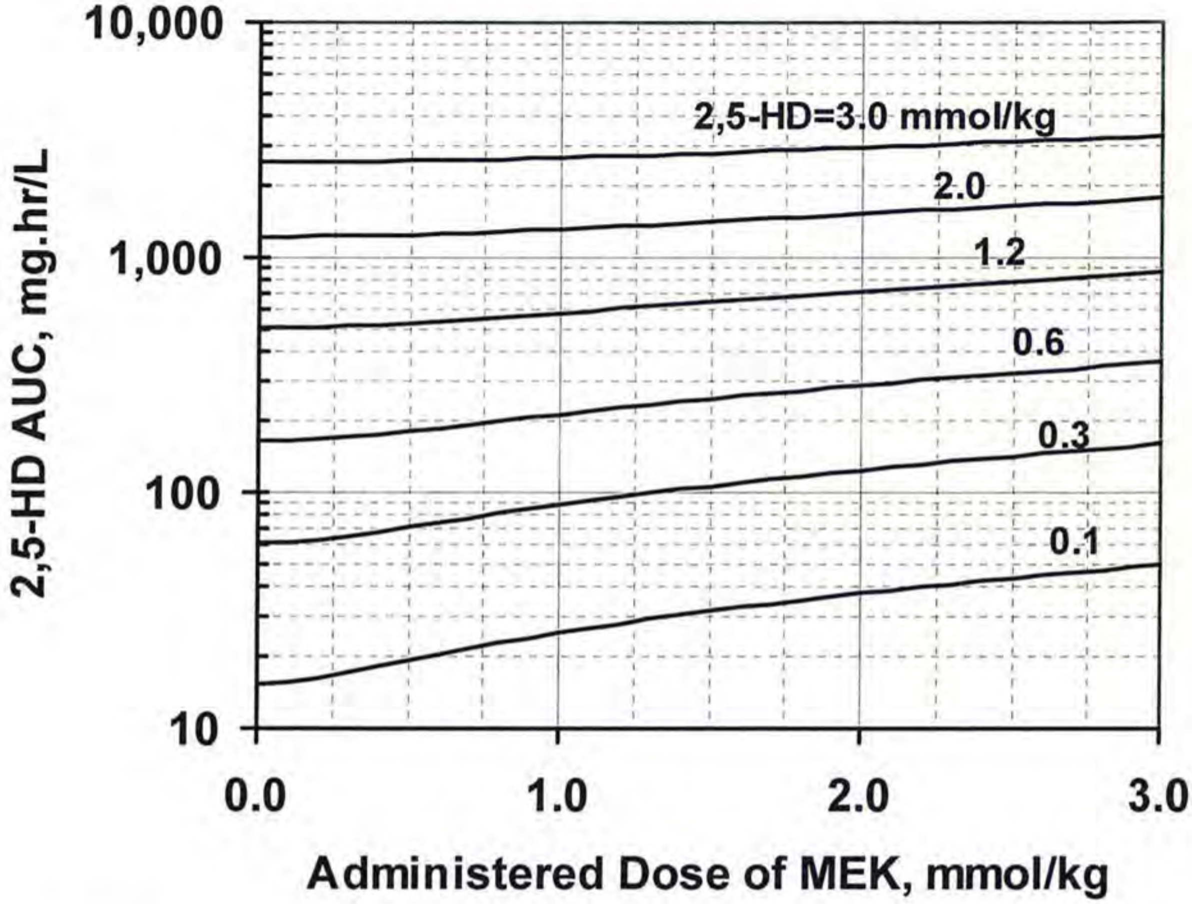

10,000
1,000
100
10
2,5-HD AUC, mg.hr/L
2,5-HD=3.0 mmol/kg
2.0
1.2
0.6
0.3
0.1
0.0
1.0
2.0
3.0
Administered Dose of MEK, mmol/kg

Figure 7

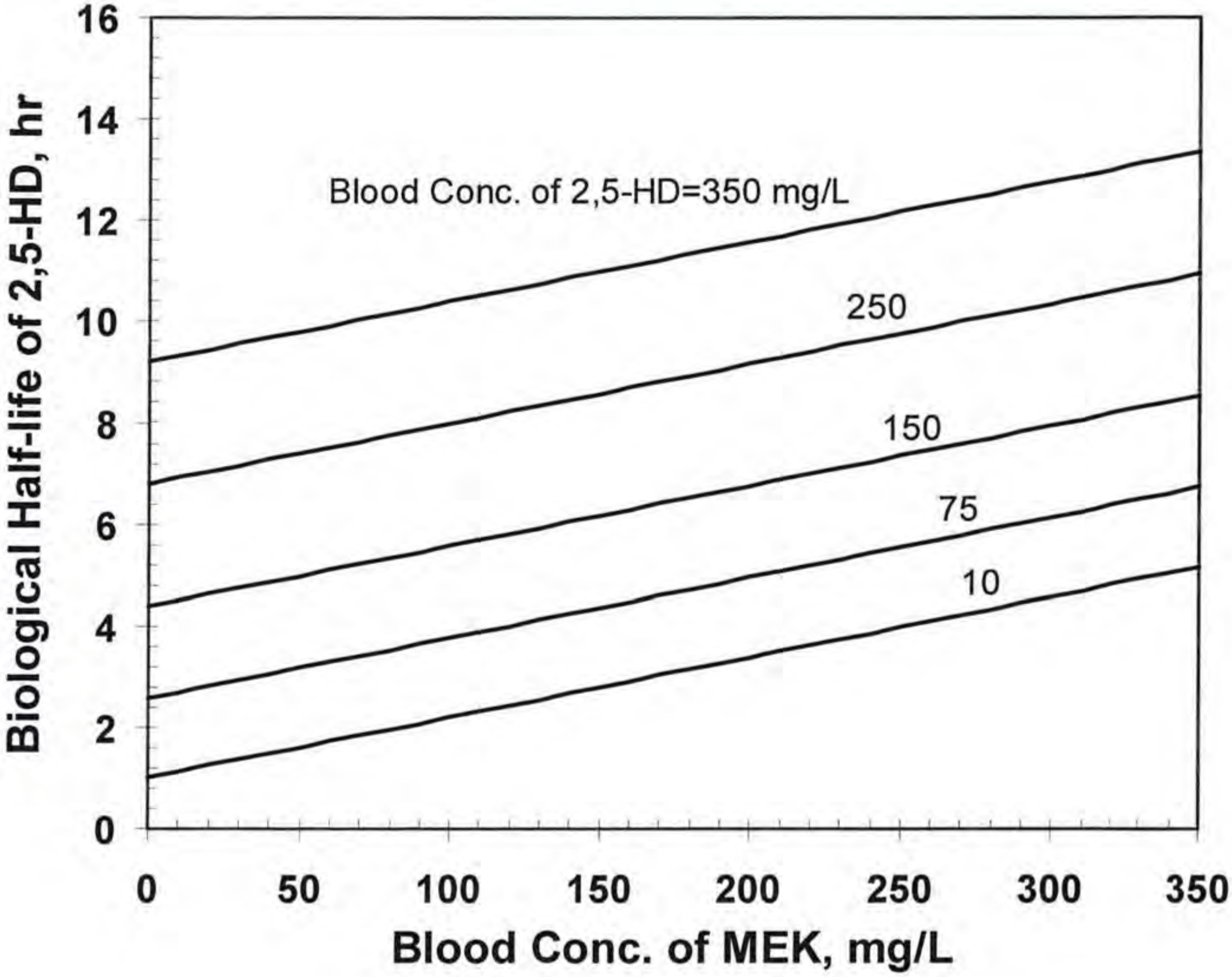

16
14
12
10
8
6
4
2
0
Biological Half-life of 2,5-HD, hr
Blood Conc. of 2,5-HD=350 mg/L
250
150
75
10
0
50
100
150
200
250
300
350
Blood Conc. of MEK, mg/L

Figure 8

Arthur Cho, Deborah Schmitz, and John R. Froines

Metabolic interaction between styrene and butadiene

Abstract

Butadiene (BD) and styrene (ST) are protoxins, i.e., compounds that are metabolically activated to toxic epoxides in a variety of tissues. In some industrial conditions, workers can be exposed to both compounds simultaneously so the nature of the metabolic interaction between the two compounds is clearly important from an occupational health perspective. Pharmacokinetic studies of the interaction between ST and BD in mice and rats showed that although ST inhibits the metabolism of BD, BD had no effect on ST metabolism. Since the toxicity of both of these compounds is dependent on metabolism, the interaction has been interpreted to reflect a "protective effect" by ST on BD toxicity by some. The compounds are converted to their toxic epoxides by enzymes of the cytochrome P450 (CYP) superfamily in what is commonly thought to be the rate limiting step in their overall metabolic transformation. To evaluate the interactions of the two compounds with CYP, we have studied epoxide formation from BD in the presence of ST and epoxide formation from ST in the presence of BD in rat liver microsomes. We considered two possible mechanisms, an irreversible one, in which the olefins could be converted to compounds capable of forming covalent bonds with the enzyme and a second possibility, that of competitive inhibition. Irreversible inhibition could be a protective action, i.e., by blocking the formation of a toxic epoxide. The results indicated that irreversible inhibition did not occur and that BD was a competitive inhibitor of ST epoxidation. These observations, made at subcellular levels, differ from the results of the *in vivo* studies, leading us to conclude that interaction at the CYP level is not the basis for the observed *in vivo* interaction. Other investigators have recently suggested that the *in vivo* interaction may involve transporters so that competition for access to the metabolic enzymes may be responsible. These subcellular studies did not address this possibility and attempts to study the interaction at the cellular level with hepatocytes were unsuccessful.

Introduction

Butadiene (BD) and styrene (ST) are protoxins, i.e., compounds that are metabolically activated to toxic epoxides in a variety of tissues (Gadberry et al 1996). Both compounds are converted to their toxic epoxides by enzymes of the cytochrome P450 (CYP) superfamily in what is commonly thought to be the slow step in their overall metabolic transformation(Nakajima et al 1993; Nakajima et al 1994; Nedelcheva 1996; Nieusma et al 1998; Vaz et al 1998). The epoxides are then hydrolyzed to the corresponding diols by the enzyme, epoxide hydrolase (Gadberry et al 1996; Kemper & Elfarra 1996; Krause et al 1997; Mendrala et al 1993), and subsequently undergo conjugation reactions before they are eliminated. In some industrial conditions, workers can be exposed to both compounds simultaneously and the nature of the metabolic interaction between the two compounds is clearly important from an occupational health perspective. Pharmacokinetic studies of the interaction between ST and BD in mice (Leavens & Bond 1996; Leavens et al 1996) and rats [(Filser et al 1993; Laib et al 1992) showed that although ST inhibits the metabolism of BD, BD had no effect on ST metabolism. Since the toxicity of both of these compounds is dependent on metabolism, the interaction has been interpreted to reflect a "protective effect" by ST on BD toxicity by some (Laib et al 1992).

The interaction of these compounds with cytochromes P450 can occur by several different mechanisms.

1. As unsaturated compounds have been shown to be irreversible inhibitors of CYP enzymes (e.g.,(Ortiz de Montellano 1986) , each could irreversibly inhibit CYP to block formation of the epoxide. In this case, formation of the toxic epoxides would be reduced and a protective effect could result.
2. If both compounds were oxidized by the same CYP enzyme, they would be competitive substrates and, depending on the values of their respective Michaelis' constants (Km), one could inhibit the epoxidation of the other.
3. A third possibility is that ST and BD epoxidation is catalyzed by different CYP enzymes so there would be no interaction on epoxide formation. This is an explanation for the inability of ST to inhibit BD metabolism by more than about 50% (Leavens & Bond 1996). In this case, interaction could take place on epoxide hydrolase, allowing the accumulation of the epoxide with lower affinity, or higher Km value.
4. Alternatively, the interaction could take place on a transporter rather than an enzyme. Laib et al., (Laib et al 1992) have suggested that the first order metabolism of BD and ST is limited by the capacity of transport processes. If competition for a common transporter is the basis for the interaction, the concentration dependency could be very complex. There are inward and outward transporters in different tissues so that interaction could take place to either increase or decrease the net inward movement of these compounds. For example, the ABC transporter, P-glycoprotein, removes lipid soluble compounds from cell membranes by outward transport. Inhibition of this transporter could actually increase the level of intracellular substrate.

To evaluate these possible interaction mechanisms at the level of cytochrome 450 enzymology, the kinetics of epoxide formation by ST and BD were determined in liver microsomes from naïve rats. The results thus far indicate that BD inhibits ST epoxidation but ST has no effect on BD epoxidation.

Materials and methods.

<u>Metabolism of Styrene in Rat Hepatocytes</u>

Primary culture incubations were conducted in 24 mL glass vials coated with collagen type 1 and sealed with Teflon-faced septa. Hepatocytes were isolated from ~200-250g Sprague-Dawley rats (Harlan) and plated at a density of 1×10^6 cells in Williams E Media containing fetal bovine serum and Streptomycin-Penicillin and allowed to grow overnight. The following day, the medium was removed and styrene, dissolved in Williams E Media, was added to initiate the metabolism. Aliquots of 100 µL of media was removed at specified time points and added to extraction tubes containing 1.5 mL hexane and internal standards, trans-ß-methylstyrene and (1R,2R)-(1)-1-phenylpropylene oxide. Samples were mixed on a vortex and centrifuged at 2000 rpm for 10 min. The hexane layer was transferred to 2mL vials. The vials were capped and stored at 4^{o} C until analysis.

Metabolism of Styrene in Rat Hepatic Microsomes

Rat microsomal incubations with styrene were conducted in 24mL glass vials sealed with Teflon-faced septa. The incubation vials were set on ice and styrene in 0.4% acetone, 0.1M Hepes buffer, pH 7.6, deionized water, rat hepatic microsomes (1 mg-1.9mg), and 1 mM cyclohexene oxide (an epoxide hydrolase inhibitor) were added to a final volume of 2 mL. The incubation mixture was equilibrated for 10 min. at 37°C and the reaction initiated by the addition of a NADPH-generating system consisting of 0.5 mM $NADP^+$, 8 mM glucose 6-phosphate, 1 unit of glucose 6-phosphate dehydrogenase and $MgCl_2$ (to a final concentration of 5 mM). Aliquots of 100 µL were removed via a gas-tight syringe extracted and with 1.5 mL of hexane containing trans-ß-methylstyrene and (1R,2R)-(1)-1-phenylpropylene oxide as internal standards. Samples were mixed on a vortex mixer and centrifuged at 2000 rpm for 10 min. The hexane layer was transferred to 2mL vials. The vials were capped and stored at 4° C until analysis.

Metabolism of Butadiene

Rat microsomal incubations with butadiene were conducted in 24mL glass vials sealed with Teflon-faced septa. The incubation vials were set on ice and 0.1M Hepes buffer, pH 7.6, deionized water and rat hepatic microsomes (1-1.8mg) in a final volume of 2 mL. Then, butadiene was added to the mixture via a gas-tight syringe and the mixture was equilibrated for 10 min. at 37°C. The reaction was initiated by the addition of a NADPH-generating system consisting of 0.5 mM NADP, 8 mM glucose 6-phosphate, 1 unit of glucose 6-phosphate dehydrogenase and $MgCl_2$ (final concentration, 5 mM). A syringe was used to remove aliquots of 0.25-0.5 mL of the incubation mixture. The aliquots were extracted with 1mL of methylene chloride containing 1, 2 epoxyhexane as internal standard. Samples were mixed on a vortex and centrifuged at 2000 rpm for 10 minutes. The aqueous layer was removed by aspiration and the methylene chloride layer was transferred to 2 mL vials.

GC/MS analysis of Styrene and Styrene Oxide

A H-P 5971A Mass Selective Detector connected to an HP model 5890 GC was used for the determination of styrene oxide. The GC/MS was fitted with a retention gap (5m, 053 mm) connected with a quartz deactivated column connector to a HP-5MS capillary column (0.25 mm i.d., 0.25 µM film thickness, 30 m length). Initial column temperature was 35°C for 0.5 min then ramped to 120 °C at a rate of 70 °C/min. Retention times for styrene, trans-ß-methylstyrene, styrene oxide and (1R,2R)-(1)-1-phenylpropylene oxide were 5.10, 7.50, 8.76 and 10.86 min respectively. The fragments monitored were m/z 104.2.0 for styrene, m/z 117.2 for trans-ß-methylstyrene and m/z 89.0 for styrene oxide and (1R,2R)-(1)-1-phenylpropylene oxide .

GC/MS analysis of butadiene monoxide

A H-P 5971A Mass Selective Detector connected to an HP model 5890 GC equipped with a cool-on-column injector was used for the determination of butadiene monoxide. The GC/MS was fitted with a retention gap (5m, 0.53 mm) connected with a quartz deactivated column connector to a HP-5MS capillary column (0.25 mm i.d., 0.25 µM film thickness, 30 m) . Initial column temperature was 35°C for 4.0 min then ramped to 100 °C at a rate of 40 °C/min. Retention times for butadiene monoxide and 1,2 epoxyhexane were 3.93 min. and 6.06 min respectively. The fragments monitored were *m/z* 39.0 for butadiene monoxide and *m/z* 71.1 for 1, 2 epoxyhexane.

Results

Hepatocyte studies

Initially, an attempt was made to utilize hepatocyte cultures as the source of tissue interaction. Hepatocytes contain the entire array of metabolic enzymes as well as membrane transporters so they would be a useful preparation in which to study details of the interactions between the two compounds.

In the initial experiments, ST was dissolved in the culture medium and incubated for 0-90 min in hepatocytes that had been cultured for 24 hours. Analysis of the medium for ST, indicated that its disappearance was linear for about 60 minutes over a concentration range between 50 and 100 μM. Accordingly, BD was added and ST disappearaance again determined. However, when BD (1000 ppm; 16 μM) was added to the hepatocytes, the cells became detached from the vials and did not survive, indicating that BD, under these conditions, was toxic to the cells. For this reason, the hepatocyte approach was abandoned in favor of a microsomal preparation. Since the slow step in the metabolic activation of ST and BD was likely to be the CYP based reaction, microsomal preparations would permit the interaction on this enzyme system.

Partition properties of BD

The gaseous nature of BD at room temperature, required an approach to determining the concentration in the incubation media based on the head space concentration. Accordingly, the partition properties of BD between head space and medium in microsomal suspensions were determined. After equilibration of BD with the microsomal preparation, head gas samples were collected from incubation vials containing 2, 5 and 10 mL of microsomal preparation after a 15 minute incubation. There was no change in concentration in the head gas, i.e., it was independent of the volume of the microsomal mixture, indicating that the aqueous concentration was equal to the head gas concentration over the range of BD used in these studies.
Based on an apparent partition of one, the concentration in the aqueous phase could be calculated from the head space concentration with the assumption of ideal gas bahavior.

Thus:

1 ppm = 1 μg/L; 1000 ppm = 1 μg /L = 1 μL/mL
Incubation vial = 24 mL; BD @ 1000 ppm = 24 μL/24mL

From ideal gas considerations:

1 mmole = 25.4 mL at 37°; 1 mL = 39.4 μmoles
1 μL = 39.4 nmoles

24 μL * 39.4 nmols/μL = 945.6 nmoles

Assuming equal distribution (Kp = 1) betweeen gas/liquid,
1000 ppm = 945.6 nmoles/24 mL = 39.4 nmoles/mL = 39.4 μM.

Then,

BD added (μL/24 mL)	ppm	microM
	1000	39.4
	5000	197
	12500	492
	50000	1970

Effect of cyclohexane epoxide (CHO) on ST to styrene epoxide (SO) formation.

We used CHO to inhibit the epoxide hydrolase present in the microsomal preparation to limit the reactions studied to epoxidation, independent of epoxide hydrolase (EH) action. CHO at 1 mM, the concentration used to inhibit EH, had no effect on SO or BMO formation from 100 μM ST and BD, respectively, the highest concentrations used.

Styrene oxide (SO) formation

The kinetics of SO formation was determined in the presence of 1 mM CHO in 15 minute incubations at ST concentrations of 5, 10, 50, 100, 200 and 500 μM. The results, determined by nonlinear regression analysis, gave a maximal velocity of 9.24 ± 2.0 nmole/min per mg microsomal protein and the concentration for half maximal velocity was 887.6 ± 278.2 μM. The Km values are much higher than those reported (Mendrala et al 1993) but those investigators used higher concentrations of acetone as a solvent for ST. There is also the possibility of multiple CYP enzymes catalyzing the reaction but the data are too limited to statistically evaluate this possibility.

Additional experiments examining the effects of a 30 minute preexposure to ST on subsequent SO formation indicated that there was no inactivation of CYP by ST.

Butadiene mono epoxide (BMO) formation

The kinetic parameters for BMO formation in liver microsomal preparations were determined at substrate concentrations between 3.9 and 197 μM. Under these conditions, the maximal velocity was found to be 3.07 ± 0.30 nmol/min*mg, and the Km, 43.00 ± 11.19 μM. The lower Km observed for BD compared to ST indicated that BD should inhibit ST metabolism at μM concentrations.

Interaction between BD and ST

The effect of varying BD concentration (98-1970 μM) on SO formation from ST at 50 μM is shown in figure 1. The data fit a competitive inhibition model, as shown in the figure with Km and Ki values of 1.62 and 7.5 μM, respectively. Thus, at these BD inhibits ST conversion to SO by a competitive process, consistent with the notion of a common enzyme, presumably a cytochrome P450 enzyme, catalyzing the epoxidation of both compounds.

However, the effect ST on BD metabolism was not consistent with this model. The effect of varying ST on BO formation at a BD concentration of 197 μM is shown in figure 2. Under these conditions, no consistent pattern of inhibition was observed.

Discussion

The interaction between ST and BD has been proposed to occur at an enzymatic and a transporter level. There are multiple transporters of xenobiotics on cell membranes that may contribute to the kinetics of different substrates. Neutral lipophilic organic compounds are common substrates for the Mdrt, or muliti drug resistant transporter (Zegers & Hoekstra 1998). These transporters move substrates from the cell membrane to extracellular space so they prevent entry into the cell. Inhibition of the transporter therefore allows greater entry into the cell by the substrate by diffusion. The transporter is present in hepatocyte membranes and could participate in xenobiotic movement. Attempts to assess the interaction at a transporter level in vitro were unsuccessful because of the toxicity of BD to the cells. We were unable to culture the cells in the presence of BD.

We then examined the interaction at the microsomal level. This preparation examines the metabolic interaction between the two compounds, and in contrast to the observations made in in vivo studies, BD inhibited SO formation but ST had no effect on BO formation. The discrepancy between the two sets of studies, may lie in the participation of transporters in the rate limiting step of BD and ST biotransformation. Furthermore, preincubation experiments indicated that neither ST no BD exhibited inactivation of CYP under the conditions used. Thus, it is unlikely that activation of either ST or BD to a CYP inhibitor takes place under the conditions of these experiments.

In vivo studies show that ST inhibits the metabolism of BD to BO [(Filser et al 1993; Laib et al 1992), but BD has no effect on SO formation. If the interaction is competitive, the competition should be mutual, i.e., either one should inhibit the other. The lack of this mutual effect suggests that a more complex interaction is occurring and that additional studies are necessary to elucidate mechanisms.

We conclude, however, that:

1. Neither ST nor BD is converted to irreversible inhibitors of their metabolizing enzyme in vitro.
2. BD appears to act as a competitive inhibitor of SO formation but ST does not affect BO formation. The interaction at the enzyme level is clearly more complex and may involve multiple cytochrome P450 enzymes. The concentration range of ST used in the metabolism covered the range found in the plasma of rats exposed to 100 μmoles/kg. Under these conditions (ST at 50 μM) BD inhibited ST epoxidation by 50% at a BD concentration of 100 μM.
3. The interaction at the transporter level should be studied in cells under conditions that minimize the direct effect of BD on cell adhesion. .

Figures

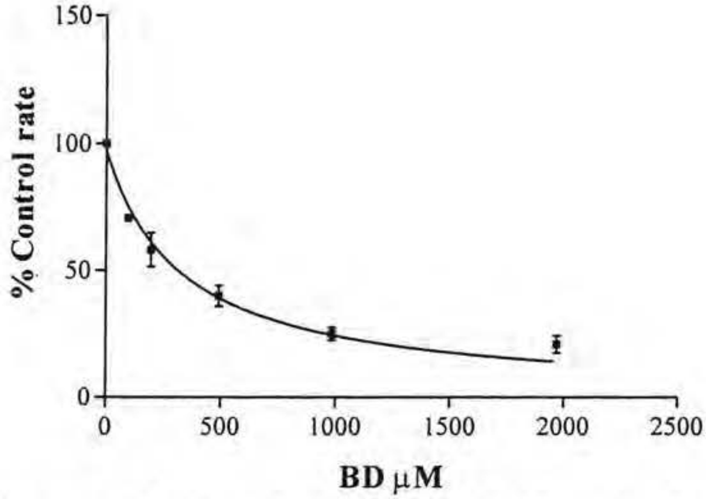
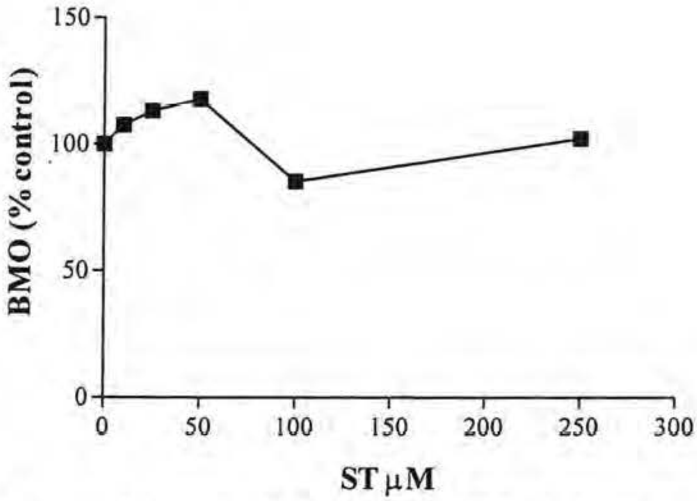


Figure 1: The effect of varying BD on SO formation from ST at 50 μM

SO concentration was determined after 15-minute incubation of ST in the presence of the indicated concentrations of BD. The data are expressed as % control (0.69 nmol SO formed /minute*mg microsomal protein). The curve represents a fit to a competitive inhibition model with the values of Km as 1.16 and Ki as 7.5 μM.

Figure 2. Effect of ST on BO formation from BD at 197 μM.



BO formation was determined in the presence of the indicated concentrations of ST. The results are expressed as percent of control activity which was 0.39 nmols/min*mg protein.

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Shachar Eylam, Dale Hattis, and John Froines

Short Term Non-Invasive Biomarkers for the Processes Producing Long Term Lung Damage--Evaluation of the Feasibility of Candidate Measurement Systems

Abstract

This report analyzes the potential for a few different potential biomarkers to serve as short term measures of ongoing chronic lung damage processes resulting from occupational exposures. We focus primarily on non-invasive measurements of ethane and pentane in exhaled air, and the urinary excretion of the elastin degradation products desmosine and isodesmosine. Excretion of the alkanes is a putative measure of oxidative processes in the lung resulting from macrophages activated by particulate exposures. Desmosine and isodesmosine are putative markers for the proteolytic processes that have been established as part of the pathogenesis of emphysema and similar conditions. For ethane we develop a physiologically-based pharmacokinetic model that can be used to interpret alveolar ethane measurements in terms of production--subtracting out the contribution of ethane stored in the body from ambient air exposures, adjusting for differences in body fat composition. A similar model for pentane is in process.

Both the ethane and desmosine/isodesmosine measurements have promise and appear feasible. Three basic suggestions are made to help assure the collection of high quality data for workers exposed to suspected lung-damaging agents:

1) For both ethane and pentane, there should be a small series of measurements of pharmacokinetic parameters both in vitro (e.g., ethane blood/air, liver/air, and related partition coefficients) and in vivo (based on measured exposures) to confirm the pharmacokinetic modeling proposed here.

2) Improved ethane (and/or pentane) ambient air measurements need to be made covering the day or two prior to breath measurements for at least a sample of study subjects.

3) Characterization of individual rates of excretion of desmosine and isodesmosine may benefit from a small series of repeated samples, spaced apart by at least a couple of weeks. Group differences, however, may well be detected by cross-sectional samples in which only a single measurement is made per person.

Introduction

By definition, chronic cumulative diseases take a long time to develop into clinically recognizable cases of impairment or illness. And therefore "clinically recognizable cases"--the usual starting point for epidemiological work--are generally years and even decades removed from opportunities for direct measurement of causally relevant exposures. It would greatly facilitate both epidemiological research and (in the long run) the targeting of possible risk control measures, if measurements could be made of the ongoing cumulative damage processes as the damage is occurring.

The potential applications of such short term measurements in epidemiology are particularly significant. Causal components of complex mixtures could be identified; effects of technical changes in the composition of the complex mixtures could be evaluated, and dose response relationships could be analyzed in ways that are just not possible if one must wait decades to observe the end effects of the pathological processes.

However, appropriate design of research in this area must acknowledge and attempt to minimize some drawbacks and hazards. In the near term, the definition of biomarkers of putative chronic cumulative processes will need to be based on our best current (albeit incomplete) understanding of the mechanisms involved. Ideally the biomarker should be highly correlated with one or more of the steps leading from external exposure to a hazardous material through the chronic accumulation of damage. Each biomarker will therefore reflect a qualitative hypothesis about the relationship between a particular kind of measurement and the cumulative pathology (see below). But there is no easy or rapid way, in the short run, to empirically verify that the measurement does in fact reflect a process that is on the causal sequence leading to pathology, or to assess the quantitative significance of particular observations for long term risk. This kind of testing of the qualitative hypotheses and measurement of long term risk implications is likely to require a long term prospective study of people exhibiting various levels of the biomarker over a defined period.* Before completion of that kind of work, it will not be possible to definitively interpret biomarker results in terms of individual risks. This fact must be made clear to all participants, particularly the subjects of the research.

The work reported here assembles information needed to design initial experimental and field trials of a few promising types of putative biomarkers of lung damaging processes:

- <u>Exhalation of ethane and possibly pentane in the breath.</u> These simple alkanes are the products of oxidation of omega-3 and omega-6 fatty acids, respectively. The primary hypothesis is that they would be a measure of relatively high levels of macrophage activity likely to result from excessive particulate loading in the deep lung, as has been observed in autopsy and bronchoalveolar lavage studies in coal miners (Rom, 1990). Auburtin et al. have recently reported relatively high levels of ethane exhalation in active underground coal miners relative to retired miners regardless of the presence of already-developed coal workers' pneumoconiosis in some of the retired miners (Table 1). (Much less impressive elevations were not seen for pentane in these worker groups--data not shown.) Lapp and Castranova (1993) have reviewed current theories on the involvement of macrophage products in the pathogenesis of both coal workers' pneumoconiosis and silicosis. In brief, phagocytically active macrophages are important both in the direct secretion of oxidants and proteolytic enzymes, and in the secretion of mediators that recruit polymorphonuclear leukocytes into the airspaces, and stimulate the release of oxidants and proteases from those cells. According to Begin et al. (1989), "...the initial early lung lesion in all mineral dust pneumoconioses is a fibrosing macrophagic alveolitis." Incidental release of oxidants can particularly be expected to result from futile attempts by macrophages to digest particles such as asbestos and silica (Archer, 1979). An additional hypothesis that also supports the potential relevance of alkane exhalation arises from observations that coal dust itself

* In the interim, another type of methodology that might produce tentative risk-related information is a case control study comparing workers of similar age and exposure who have and have not developed one of the pneumoconioses in question. For an example application to the release of TNF from blood monocytes by coal dust, see Borm et al. (1990). The difficulty with this approach is that altough it can provide some tentative indications of an association between a biomarker and a disease, it can be difficult to tell whether an elevated level of the biomarker is (1) a predictor of early effect or susceptiblity, or (2) a later consequence of the disease process.

appears able to generate hydroxyl radicals from hydrogen peroxide and induce lipid preoccupation in vitro (Dalal et al., 1995). This activity appears to be related to the surface iron content of the coal particles. If it were found that this is reflected in *in vivo* lipid peroxidation it could provide a specific physical/chemical measurement that might ultimately be useful in targeting control measures. Concentrations of stable coal borne free radicals are associated with the severity of coal workers' pneumoconiosis in lung tissue samples from deceased coal miners (Dalal et al., 1991). Related mechanisms have been documented for silica particles (Ghio et al., 1990) and asbestos Kamp et al. (1992).

- Urinary excretion of breakdown products of elastin (desmosine and isodesmosine) and collagen (hydroxyproline). These biomarkers are hypothesized to reflect excessive amounts of proteolytic activity in the lung. Excessive proteolysis has previously been associated with elevated risk of emphysema in humans by observations of the effects of genetic variants of alpha-1 antitrypsin--a protease inhibitor that is important in protecting lung tissue against neutrophil elastase (Evans and Pryor, 1994; Gadek, 1992; Tockman et al., 1993).* Inactive forms of this protease inhibitor cause several fold elevations in susceptibility to emphysema among smokers (Kalsheker, 1994; Shimizu and Mizunuma, 1991). More recently, work in rats has shown that crystalline silica, but not the relatively benign particulate titanium dioxide, induces a sustained elevated release of desmosine and hydroxyproline into bronchoalveolar lavage fluid, apparently in parallel with the presence of increased numbers of polymorphonuclear lymphocytes (Li et al., 1996). In addition to the possible action of silica in stimulating cellular release of proteolytic enzymes, freshly ground silica can apparently directly inactivate alpha-1 antitrypsin via an oxidation-dependent mechanism (Zay et al., 1995).

- A few other biomarkers that have been proposed based on measurements in plasma (Porcher et al., 1993). The most promising of these as measures of current exposure and possible contributions to long term pathological processes are leukocyte elastase (HLE), plasma neutral metalloendopeptidase elastase type (NMEP), and fibronectin (FN). All three biomarkers have been observed to be increased in coal miners as compared to control workers without mine dust exposure. HLE and NMEP are possible measures of elastase proteolytic activity, and thus reflect the same causal hypothesis as the urinary desmosine/isodesmosine measurements discussed in the previous bullet. [Most recently, a 5-7 fold increase in NMEP in active coal miners has been confirmed in further work (Soleihac et al., 1996)]. Fibronectin is reportedly involved in the recruitment and proliferation of fibroblasts during firbrogenesis (Ruoshlati, 1988).

* Neutrophil elastase is the basis of a well known experimental model of emphasema on tracheal instillation in animals (Mauderly et al., 1989). In humans, smoking has been shown to increase the local retention of externally-supplied neutrophils in the lung (MacNee et al., 1989).

Table 1
Measurements of Ethane in the Breath of Active and Retired Coal Minters--Data of Auburtin et al.

A. Results Stated In Terms of Ethane Production Rate (pmole/min)

	Gmean current dust exposure (μg/m^3	N	Ethane production rate (pmol/min) Geom mean	GSD
Surface workers	**0.31**			
Smokers		15	147	1.9
Nonsmokers		15	57.9	2.6
Total		30	92.3	2.5
Underground miners	**1.61**			
Smokers		15	307	1.7
Nonsmokers		17	469	7.3
Total		32	384	4.4
Retired miners (- pneum)	**0**	38	58.5	2.5
Retired miners (+ pneum)	**0**	25	44.1	3

B. Results Stated In Terms of Alveolar Air Ethane Concentration (pmol/liter)

	Gmean current dust exposure (μg/m^3)	N	Ethane concentration (pmol/liter) Geom mean	GSD
Surface workers	**0.31**			
Smokers		15	209	2.1
Nonsmokers		15	104	2.2
Total		30	147	2.3
Underground miners	**1.61**			
Smokers		15	437	1.8
Nonsmokers		17	614	7.3
Total		32	523	4.4
Retired miners (- pneum)	**0**	38	90	2.3
Retired miners (+ pneum)	**0**	25	90.1	2.4

Section 2 below will first give a basic technical description of the three types of assays, and generally assesses their feasibility. For the urinary measurements of desmosine and isodesmosine, this will include our limited information about the dynamics of change following an unusual high-elastin meal. Section 3 will then describe a preliminary physiologically-based pharmacokinetic model for ethane that assess the needs for different types of washout times to avoid confusion between internally-generated ethane and ethane absorbed from the external air.

Initial adaptation of this modeling framework to pentane will also be discussed. Finally, the concluding section will make recommendations for the design of preliminary laboratory and field studies to develop these biomarkers.

Basic technical description and feasibility of measurements in exposed workers

Breath Alkane Measurements

There are now nearly two decades of published reports of breath pentane and ethane output as measures of lipid peroxidation in vivo (Wade and van Rij, 1985; Morita et al., 1986; Dilard et al, 1978). More recently, measurements of breath pentane have been controversial (Springfield and Levitt, 1994). There have been very wide differences (reportedly over 1000-fold) among different laboratories in reported background pentane levels (our own summary is reproduced in Table 2). Some of the differences probably arose because of the similar retention times of pentane and isoprene in many gas chromatography system. Isoprene is evidently present normally in expired air in about 20-fold larger concentrations than pentane (Kohlmuller and Kochen, 1993), and it migrates at a similar rate in many commonly used gas chromatography systems, making it likely that some past researchers have recorded appreciable amounts of isoprene as pentane. This appears especially likely for researchers who have reported the greatest outputs of pentane (e.g., Zarling and coworkers). In experiments with authentic reference materials, pretreatment with aqueous potassium permanganate removed all the isoprene but did not alter pentane concentrations. When the same potassium permanganate treatment was applied to alveolar breath samples it was possible to greatly reduce the previously apparent "pentane" peak leading to the conclusion that this material was in fact isoprene (Springfield and Levitt, 1994).

A final concern raised by Springfield and Levitt is that past researchers have used different and generally inadequate periods of time breathing low-hydrocarbon air for "washout" of stored pentane from fat tissue. In experiments in rats, they measured the rate of decline in expired pentane after 20-hour exposures to high levels (2,000-4,000 ppm) of pentane in external air.

For normal rats (7% fat), they report recovery of about 64 μmoles/kg body weight of pentane under these conditions--including 24 μmoles/kg body weight in a relatively slowly-exchanging compartment (half life of about 2.8 hours) that they identify as likely to be fat. For an obese strain of rats (Zucker--50% fat tissue) a total of about 630 μmoles/kg body weight were stored and later recovered, including 520 μmoles/kg in a slow exchanging compartment with a half life of 8.5 hours (Table 3). The rather dramatic conclusion of this paper is an expression of doubt that endogenously generated pentane has ever been accurately measured in people.

This issue should eventually be addressed by the development of a full PBPK model for pentane. It should be noted here, however, that the ratio of recoverable stored pentane per body weight per ppm of external exposure in these rat experiments gives us a starting point for reasoning about how much pentane could potentially be stored and re-released in humans exposed to normal ambient background pentane. This background is reported to be of the order of 2.4-7.6 ppb in urban outdoor air--corresponding to 110-340 pmol/liter. This is somewhat more than the average of about 134 pmol/liter reported by Kohlmüller and Kochen (1993) or the potentially somewhat higher concentrations in the environment of mine workers (for which data will need to be gathered). Another implication of these findings is that regardless of the pharmacokinetic modeling that is possible based on existing data, there should at least be some preliminary uptake and re- release experiments with ethane and pentane in humans with concurrent estimation of body fat via skinfold thickness measurments.

Kohlmüller and Kochen (1993) report finding an appropriate method to be used in humans in order to isolate ethane and pentane; it is based on cryofocusing (a gas trapping system that focuses the organic volatile components of the air using a helically formed glass-lined tubing immersed in liquid nitrogen at one end to avoid occlusion by CO_2 and water) in combination with gas chromatography and is adaptable to mass spectrometry. The column they recommend for separation of *n*-pentane and isoprene is a Poraplot U column from Chrompack (Kohlmüller and Kochen, 1993). Unfortunately, while these authors are exquisitely attuned to the precautions needed for accurate analytical chemistry in measuring pentane, they do not appear to have taken the same care on the biological/pharmacokinetic side. They do not report using a "washout" period with low-hydrocarbon air to reduce the contribution of pentane stored in the body from prior exogenous exposures. And although their results for each person reflect 3-8 replicate chemical measurements, they do not appear to have collected replicate samples to assess the stability of the pentane exhalation measurements within study subjects. Finally, at least with the relatively small volumes of expired gas they analyze, their system is apparently not sensitive enough to measure ethane levels.

Table 2
Overview of Past Measurements of Ethane and Pentane in Exhaled Air

Reference	Condition	Ethane	Pentane
Refat '91	in children with vitamin E deficiency	Control: 31 ± 12 pmol/kg/min Patients: 78 ± 10 pmol/kg/min	
Habib '95	in adults	Background (air): 6.64 ± 0.33 pmol/L Nonsmokers: 0.59 ± 0.18 pmol/min/kg Smokers: 2.9 ± 0.52 pmol/min/kg Ex-smokers: 1.55 ± 0.36 pmol/min/kg	
Pincemail '90	exercise		At rest: 4.13 ± 2.14 pmol/L After exercise: 17.1 ± 7.73 pmol/L w/propranolol: At rest: 1.76 ± 0.77 pmol/L Exercise: 5.93 ± 5.76 pmol/L
Wade '85	in healthy adults	95.1 ± 19 pmol/h/kg (~1.6 pmol/min/kg)	

Zarling '92	in healthy adults	Results: 0.41 ± 0.32 nmol/L Normal: 0.8 ± 0.39 nmol/L	Results: 4.3 ± 1.7 nmol/L Normal: 3.7 ± 1.2 nmol/L
Seabra '91	in control subject	2×10^{-9} moles/kg/min	1.5×10^{-9} moles/kg/min
Kohlmüler '93	in control subject		0.022 — 0.377 nmol/L (isoprene: 0.27—3.13 nmol/L)
Massias '93	in control subject	4.83 ± 3.0 nmol/L	3.16 ± 2.05 nmol/L
Van Gossum '92	in adults		Nonsmokers: 5.82 ± 0.46 pmol/kg/min Smokers: 12.8 ± 1.43 pmol/kg/min
Euler '96	in adults		Nonsmokers: 0.23 ± 0.3 nmol/L Smokers: 0.17 ± 0.03 nmol/L Ambient air: 0.05 ± 0.01 nmol/L Mainstream smoke: ND (<0.02 nmol/L)

Table 3
Metabolism vs. Uptake Of Environmental Pentane In The Rat (Data of Springfield and Levitt, 1994)

Types of rats	Uptake of pentane over 20 hrs (pmoles/kg)	Pentane Recovery (pmol/kg) Lungs	Slowly equilibrating tissues (fat)	Rapidly equilibrating tissues
Normal	900	0.62	24 ± 2	39 ± 4
Zucker (obese)	1020	0.57	520 ± 70	110 ± 20

Mean ± SEM

Clearly, however, before any field measurements of pentane are undertaken, there will need to be a reasonably extensive series of preliminary analytical chemistry and human experimental pharmacokinetic observations using controlled exposures and washout periods in order to establish the fundamental validity of the measurement system.

It should be noted that the objections expressed by Springfield and Levitt are directed exclusively at pentane measurements. Ethane, being much lighter, is likely to be stored in fat to a much lesser extent relative to the amount exhaled. Ethane also has the advantage of being much less readily metabolized, leading to reduced complications with interindividual variability in metabolic elimination. For these reasons Habib and coworkers have chosen to use exhaled ethane as the focus of their studies in cigarette smokers and controls with and without antioxidant supplementation (Habib et al., 1995; Do et al., 1996).

Habib et al. use a relatively short 2-4 min. period of washout with low hydrocarbon air (6.64 ± 0.33 pmol/liter of ethane) before collecting timed 2-minute samples of expired air. (In all cases this background concentration of ethane is subtracted from the measured values.) After collection and mixing, approximately 12 liters of the contents of the collection bag are passed through duplicate cold traps of freshly prepared activated charcoal immersed in frozen ethylene glycol at -70 ^{o}C (so that each cold trap gets about 6 liters of expired air). The remaining volume of expired air is then measured with a spirometer. The charcoal from each trap was placed in a test tube with an open screw top, and heated for 3 min. at 250 ^{o}C with agitation. 5 ml samples of the headspace from these tubes were then injected into a gas chromatography system (2 meter glass column packed with Carbosphere 60/80 at 220 ^{o}C and eluted with helium at 25 ml/minute. The retention time of ethane under these conditions was 4.74 min. The subjects were requested not to eat or smoke for at least an eight-hour period prior to the measurements.

Our analysis of data extracted from the figures shown in Habib et al. (1995) indicates a short-term half-life for ethane exhalation following the smoking of a single cigarette by smokers is about 0.53 hrs (32 min) while the corresponding value for nonsmokers is 0.146 hrs (about 9 min). [Caveat, this estimate of the rate constant is likely to be too low because the calculations ignored the large variation for values at Time 0 (cigarette smoking time) for both smokers and nonsmokers (mean pmol/min-kg ± SEM: 24.5 ± 5.33 and 12.9 ± 4.1, respectively), and therefore the half life may be shorter than indicated.]

Overall, this initial paper indicates greater baseline excretion of ethane in smokers (2.90 ± .52 pmol/min-kg than either nonsmokers (1.11 ± 0.26; p = .0064) or ex-smokers (1.55 ± .36 pmol/min-kg; p = .044). This initial result is therefore promising--suggesting that current smoking is associated with excess ethane exhalation that could reflect some ongoing excess of oxidative activity in the smokers (assuming, for the moment, that residual stored ethane from 8+ hour past smoking is not contributing significantly to the observations). Lognormal Z-Score plots of these data as extracted from figures in the manuscript are shown in Figure 1. The data indicate rather more variability in the measurements for nonsmokers (steeper slope) probably because of a combination of less precise measurements at the lower levels of excretion (particularly in the one isolated point to the extreme left in the nonsmoker plot), and greater difficulty in reading the nonsmoker points from the graph in the paper.

These initial results have been followed up in a subsequent paper testing the effects of antioxidant supplementation on ethane exhalation in 10 smokers and a more limited group of 3 non-smokers (Do et al., 1996). In brief, Do et al. (1996) find that supplementation with a combination of the antioxidants beta-carotene, alpha tocopherol, and vitamin C modestly but significantly reduces ethane exhalation among the smokers (from 4.06 ± 1.49 [SD] pmol/kg-min to 2.90 ± 1.29 pmol/kg-min). (Lognormal probability plots of these data are shown in Figure 2.) There was no comparable finding in the very small group of non-smokers. Moreover after the supplementation, there was a significant positive relationship between ethane exhalation and the ongoing smoking rate in packs per day. Finally, there was a curious finding that the degree of reduction of ethane exhalation levels with antioxidant supplementation was greatest in those smokers who had the worst lung function as measured by % Predicted FEV. Such a result, suggesting a greater benefit of supplementation associated with putatively greater accumulated damage from past smoking is almost too good to be true, especially considering the very limited sample size on which it is based. Overall, the preliminary Do et al. (1986) findings tend to support the notion that ethane exhalation, as they measure it, is related to oxidative processes that are in turn related to smoking.

In conclusion, measurement of ethane in expired air shows some initial promise as a measure of oxidative processes that might be occurring at larger than normal rates in both smokers and coal miners. However, each of the sets of data has its difficulties that need to be worked out in further preliminary studies. The Aubertin data quoted in Table 1 on their face appear to provide support for both the effects of cigarette smoke and coal dust on ethane exhalation--both qualitatively and quantitatively. However there was no description of a washout procedure in the brief report of this study, and data have some internal difficulties. If one divides the reported ethane production rates (pmole/min) by the reported air concentrations (pmole/liter), the implied alveolar ventilation rates range from about 0.5 to 0.75 liters per minute--about ten fold too low. This reduces confidence in the accuracy of the absolute values reported. Probably it would be prudent to confer with the Auburtin group to resolve this problem before making comparisons with the Do et al findings. It would also be advisable to contact and possibly visit the Habib/Do group (in Arizona) to learn of any further work that may now be in press, and to get information about any experimental assay details that are not fully described in the paper.

Figure 1

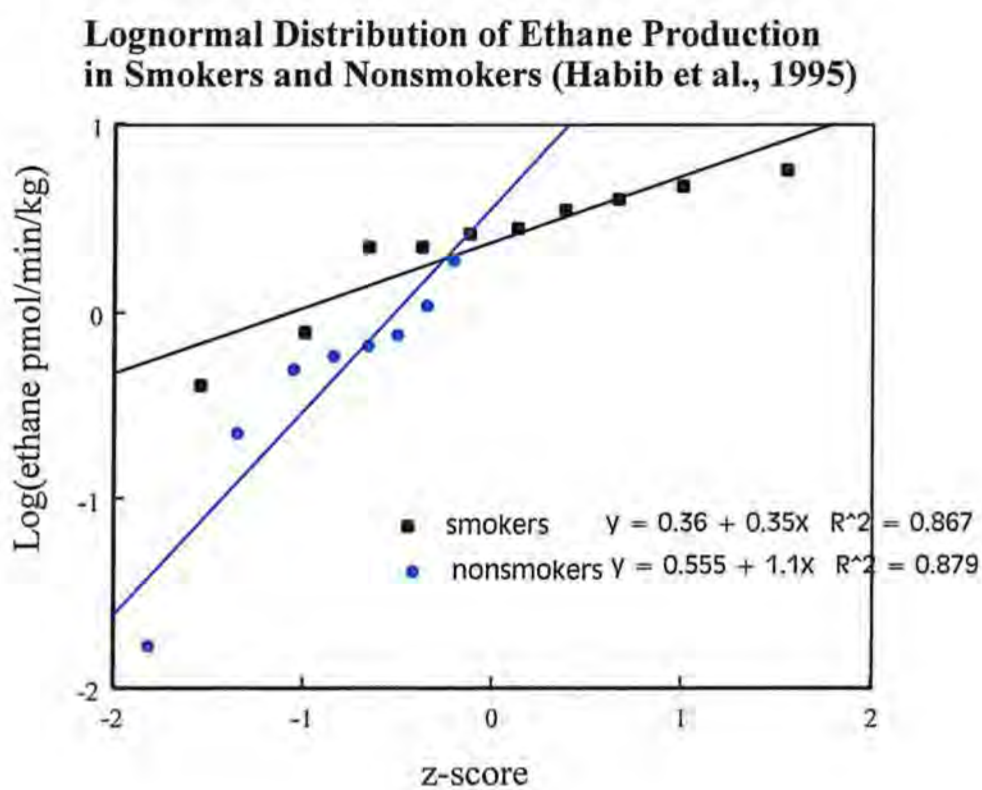
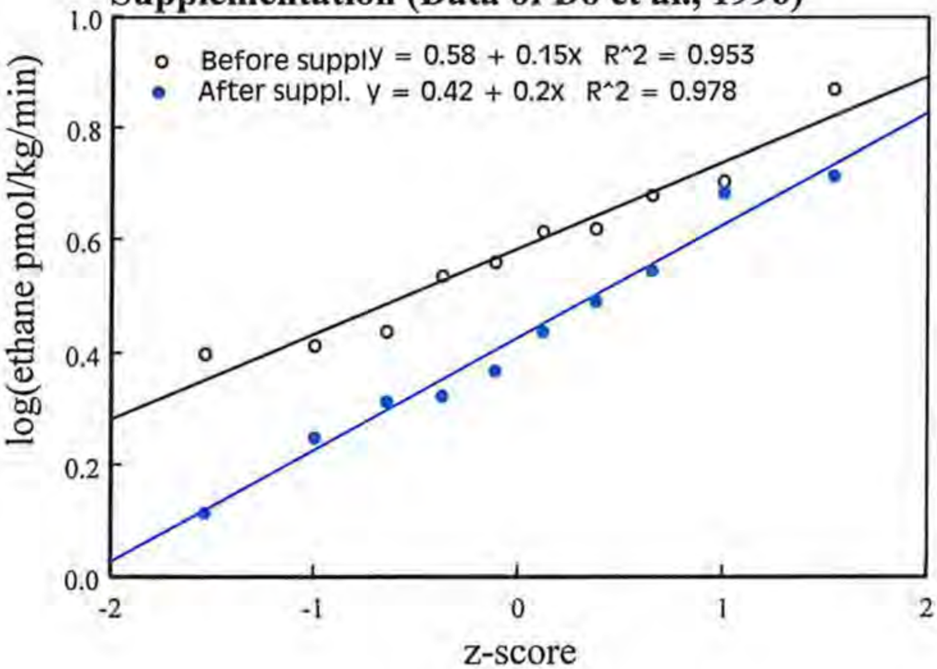


Figure 2

Lognormal Distribution of Exhaled Ethane Levels of Smokers Before and After Vitamin E Supplementation (Data of Do et al., 1996)



A final possibility that merits exploration is the possibility of single-breath measurements of alkane exhalation by a portable field mass spectrometry system described by Karla Thrall of the Battelle Pacific Northwest National Laboratory* (Richland Washington) at a recent DOE-sponsored conference on biomarkers (Thrall and Kenny, 1997).

Urinary Measurements of Elastin and Collagen Breakdown Products

The single most helpful papers for guiding the design of specific measurement procedures for urinary desmosine and isodesmosine are Cumiskey et al. (1995), and Stone et al. (1994, 1995). Both groups first collect 24-hour urine samples. (There does not seem to be any reason in principle why shorter collection periods or spot samples could not be used, with creatinine correction, but sampling variability might well be increased with less than 24 hour samples. The analytical procedure was routinely done on 24 ml volumes of urine). Then there is a hydrolysis step with strong acid (6 M HCl), followed by removal of interfering compounds with fibrous cellulose powder columns, and finally HPLC separation and quantification by absorption of ultraviolet light at characteristic frequencies. The Cumiskey et al. paper provides a very detailed protocol. The limit of detection is reportedly about 30 pmol--equivalent to about 2 pmol/ml in unhydrolyzed urine.

* Telephone: 509-375-6702.

Table 4 shows the basic results of Cumiskey et al. in which a total of six urine samples from three subjects were analyzed on two different days. The comparison of the measurements on the two different days gives us a measure of the experimental reproducibility (coefficient of variation = 16-21%; the comparison of average results for each subjects gives an approximate measure of the interindividual variability [coefficient of variation = 14-32%; or, in logarithmic terms log(GSD) = .064-.13)]. In the light of the observed day-to-day variability in the assay, the authors advise that several days of sampling should be used to characterize elastase activity in individual people.

Table 4
Inter-Assay Variability in Desmosine and Isodesmosine Concentration Measurements in Urine Samples from Healthy Subjects--Data of Cumiskey et al. (1995)
(concentrations in pmol/mg creatinine)

A. Individual Sample Data

subject	sample	IDES-day 1	IDES-day 2	DES-day 1	DES-day 2	IDES+DES-day 1	IDES+DES-day 2
11	A	7.06	7.06	10.43	7.34	17.49	14.40
11	B	6.99	8.00	7.58	9.55	14.57	17.55
12	C	10.27	9.67	7.92	8.12	18.19	17.79
12	D	12.74	14.03	10.12	12.08	22.86	26.11
13	E	4.52	6.10	5.06	6.47	9.58	12.57
13	F	7.61	8.08	8.52	8.88	16.13	16.96

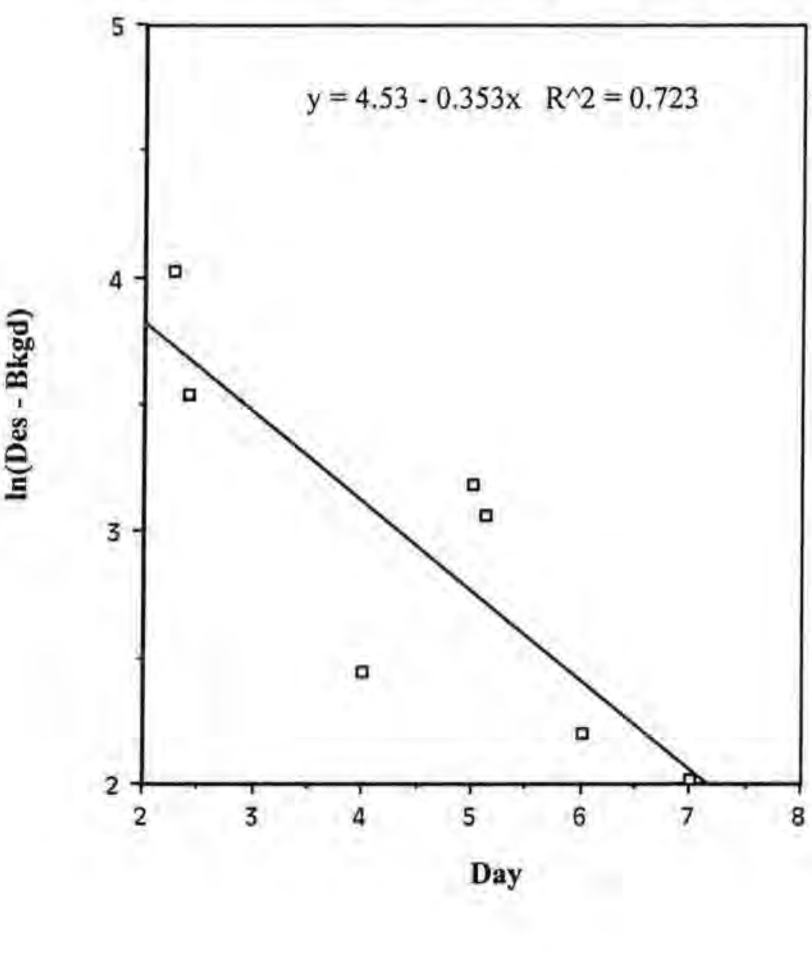
B. Summary Data for all Measurements for Each Subject

Subject	Mean IDES	Std error IDES	Mean DES	Std error IDES	Mean DES + IDES	Std error IDES
11	7.28	0.24	8.73	0.75	16.00	0.88
12	11.68	1.03	9.56	0.98	21.24	1.99
13	6.58	0.81	7.23	0.90	13.81	1.70
Interindividual Coefficient of Variation (%)	32		14		22	
Interindividual Log(GSD)	0.134		0.064		0.097	

Another reason for sampling on multiple occasions is that the elimination of desmosine from the system appears to be relatively slow. Stone et al. (1994) followed the excretion of desmosine following the ingestion of a special elastin-rich meal (300 g of calf ligamentum nuchae, containing 100 g of elastin, including 1.5 grams of desmosine and 1.2 g of isodesmosine. With a 1-2 day delay (presumably for absorption), this caused 8-10 fold increases in daily excretion of the two elastin derivatives per g of creatinine. (By contrast a 1 lb meal of ground beef led to only about a 28% increase, after correction for creatinine, which was not statistically significant). After reaching a peak, there was a prolonged period of fall in desmosine excretion, apparently with a half-life of about 2 days (Figure 3). Stone et al. (1994) suggest a prolonged process of absorption in this experiment in part on the basis of earlier measurements of an elimination half-life of about 3 hours from the systemic circulation (Pai et al., 1991). On the other hand, Stone et al. (1995) have successfully used spot urine samples in 22 never-smokers, 13 smokers, and 21 patients with Chronic Obstructive Pulmonary Disease to characterize group differences. The latter two groups had approximately a 50% increase in desmosine and isodesmosine excretion compared to the never-smokers. Based on an approximate 74-year half-life of lung parenchymal elastin, they estimate that in never-smokers normal degradation of lung elastin accounts for about 19% of urinary desmosine. On this basis they estimated that their observations of excess desmosine excretion in smokers would be consistent with approximately a three-fold increase in

Figure 3

Log-Linear Plot of the Decline of Excess Excretion of Urinary Desomosine Following a High-Elastin Meal [Combined Data for Subjects 4 and 10 of Stone et al. (1994) After Subtraction of Background]



the rate of degradation of lung elastin. The results for COPD patients were interpreted as indicating a somewhat larger increase in baseline lung elastin turnover in that group.

In conclusion some surveys of urinary desmosine and isodesmosine excretion seem possible based on spot urine samples of workers with current or past high occupational particulate exposures.

Pharmacokinetics/pharmacodynamics of changes in measured alkane exhalation rates
In this section we address the issue of tissue storage and re-release of ethane and pentane. We do this by constructing physiologically-based pharmacokinetic models (as best we can from the available data) and simulating the time course of ethane excretion following an abrupt change from ambient hydrocarbon levels to those present in relatively low hydrocarbon air. (Later work could apply this approach to pentane). Given this, we ask:

- Are procedures such as those of Habib et al. (1995) and Do et al. (1996) sufficient to ensure that there is negligible interference from stored ethane (or pentane)?
- What "washout" periods are advisable?
- Under what circumstances of background ethane/pentane exposure is it likely to be necessary or helpful to measure body fat content to aid in separating out stored/rereleased hydrocarbons from hydrocarbons that are generated by ongoing oxidative processes?

Breath Alkane Pharmacokinetic Measurements Useful for Model Calibration
By far the most useful information for pharmacokinetic modeling of ethane and pentane is contained in some early papers by Wade and Van Rij (1985) and Van Rij and Wade (1987). The former paper has measurements of the "solubility coefficients" of ethane and pentane in various tissues based on an apparently conventional vial headspace equilibration technique (Table 5). We interpret these as tissue/air partition coefficients.

Table 5

Tissue/Air Partition Coefficient Measurements (Mean ± SD; N = 4) Reported by Wade and Van Rij (1985)

Gas	Fat	Muscle	Viscera
Ethane	2.7 ± 0.2	< 0.05	< 0.05
Propane	7.3 ± 0.5	0.4 ± 0.1	0.8 ± 0.2
Butane	17.0 ± 2.9	1.9 ± 0.4	2.0 ± 0.5
Pentane	37.5 ± 5.2	3.0 ± 0.6	5.8 ± 1.2

From these coefficients and unstated assumptions about body composition, these authors calculate overall body tissue/air coefficients of 0.44 for ethane and 8.4 for pentane. These numbers are similar to values calculated earlier by Filser et al. (1983) for rats--(0.61 for ethane and 5.46 for Pentane).

For pentane, we can compare the Wade and Van Rij measurements with a more extensive set of measurements made by Perbellini et al. (1985) in tissues from two men who had died sudden deaths (Table 6). It can be seen that the fat/air values for pentane compare very well. There is, however considerable divergence for muscle/air. Muscle partition coefficients are notoriously difficult to measure because the fibrous nature of the tissue may impede equilibration. Less understandable is the apparent divergence for "Viscera" (corresponding to the "Vessel Rich Group in conventional Physiologically Based Pharmacokinetic Modeling). If we average the liver/air, kidney/air, and brain/air values of Perbellini, we obtain a value of 1.63-- which, like the muscle value, is less than a third of the corresponding tissue/air partition coefficient for "viscera" given by Wade and Van Rij. (1985). The Perbellini et al. observations indicate tissue/blood partition coefficients of 104, 5.53, 4.3, and 1.83 for fat, liver, VRG, and muscle, respectively.

Table 6

Tissue/Air and Blood/Air Partition Coefficient Measurements (Mean ± SD) for Pentane Reported by Perbellini et al. (1985)

Oil	47 ± 2.3
Blood	0.38 ± 0.08
Liver	2.1 ± 0.9
Kidney	0.6 ± 0.3
Brain	2.2 ± 0.5
Fat	39.6 ± 2.6
Muscle	0.7 ± 0.4
Heart	0.2 ± 0.4
Lung	0.5 ± 0.03

Beyond the information on partition coefficients, The Wade and van Rij papers report results from experiments in which six healthy subjects were attached to a rebreathing circuit containing a 14 liter spirometer after a preliminary "washout" period of 1.5-2 hours during which subjects were exposed to air containing very low levels of hydrocarbons (<1 pmol/liter). Rates of production of ethane and pentane were measured in this system over a two-hour period. In later studies (Van Rij and Wade, 1987) the rebreathing system was initially charged with a known high hydrocarbon concentration 41-45 nmol/liter), and the fall in ethane and pentane levels was followed over time. Experiments in this system with and without inhibition of metabolism (by dithiocarb; dosage not specified) allowed the authors to make estimates of metabolic rates. The authors' summary estimates of the relevant pharmacokinetic parameters in these papers are shown in Table 7.

Development of a Physiologically Based Pharmacokinetic Model for Ethane

Model Structure and Exogenous Parameter

We implemented a standard PBPK model structure in the Stella dynamic modeling language (Hattis, 1991). "Compartments" were specified as the Liver, Fat, Muscle Group ("poorly perfused" in other work), and the Vessel Rich Group ("richly perfused" in other work). As is conventional, full equilibration was assumed between each tissue and the blood flowing through each tissue, and between alveolar air and arterial blood. To increase speed, the lung was not included as a storage compartment, but exchange was modeled as a dynamic equilibrium between alveolar air and arterial blood. The Stella model diagram is given in Figure 4; equations for the ethane model are summarized in Table 8. Human tissue volumes and flow rates are taken from our earlier work (Hattis, 1991; Hattis et al., 1986).

Table 7
Key Pharmacokinetic Summary Observations of Wade and Van Rij (1985) and Van Rij and Wade (1987) Used for the Development of Our PBPK Models

Parameter	Ethane	Pentane
Half-life with metabolism intact	3.6 hours (87 paper) 4.1 hours (85 paper)	45 min (87 paper) 52 min (85 paper)
Half life after inhibition of metabolism	6.2 hours	2 hours
Production Rate (pmoles/kg BW-hr ± SD)	95.1 ± 19.0	not given
Concentration in rebreathing system after 2 hours, with metabolism intact (pmole/liter)	370	120 ± 50
Concentration in rebreathing system after 2 hours, with inhibition of metabolism (pmole/liter)	622	1,600

Fitting Values of Key Unknown Parameters

For ethane, the key parameter that is missing from the available data is the blood/air partition coefficient. To estimate this, and corresponding values for tissue/blood coefficients, we set up a structure in which the model parameters for all of the tissue/blood partition coefficients depended on a specific trial value for the blood/air coefficient (see diagram and equations--we tentatively treated the "< .05" estimates of tissue/air for viscera and muscle as equal to .05). By running a small series of simulations,[1] we found that a blood/air partition coefficient of 0.105

[1] For these simulations, the model first was allowed to approach dynamic equilibrium with 1000 minutes of running under baseline conditions (external air concentration = 374 pmoles/liter; production of ethane = 111 pmoles/min). Then external exposure, ethane production and metabolism were turned off, and the half life for the decline in the ethane exhalation rate was measured in 20 minute periods beginning at t = 20 minutes after the change:

Time after shutoff of metabolism, production, and external exposure (min)	Elimination half life (hrs) measured over 20 min periods beginning at the times indicated
20	1.0
40	5.5
60	6.3
80	6.4
100	6.3

Figure 4

Ethane Model Diagram

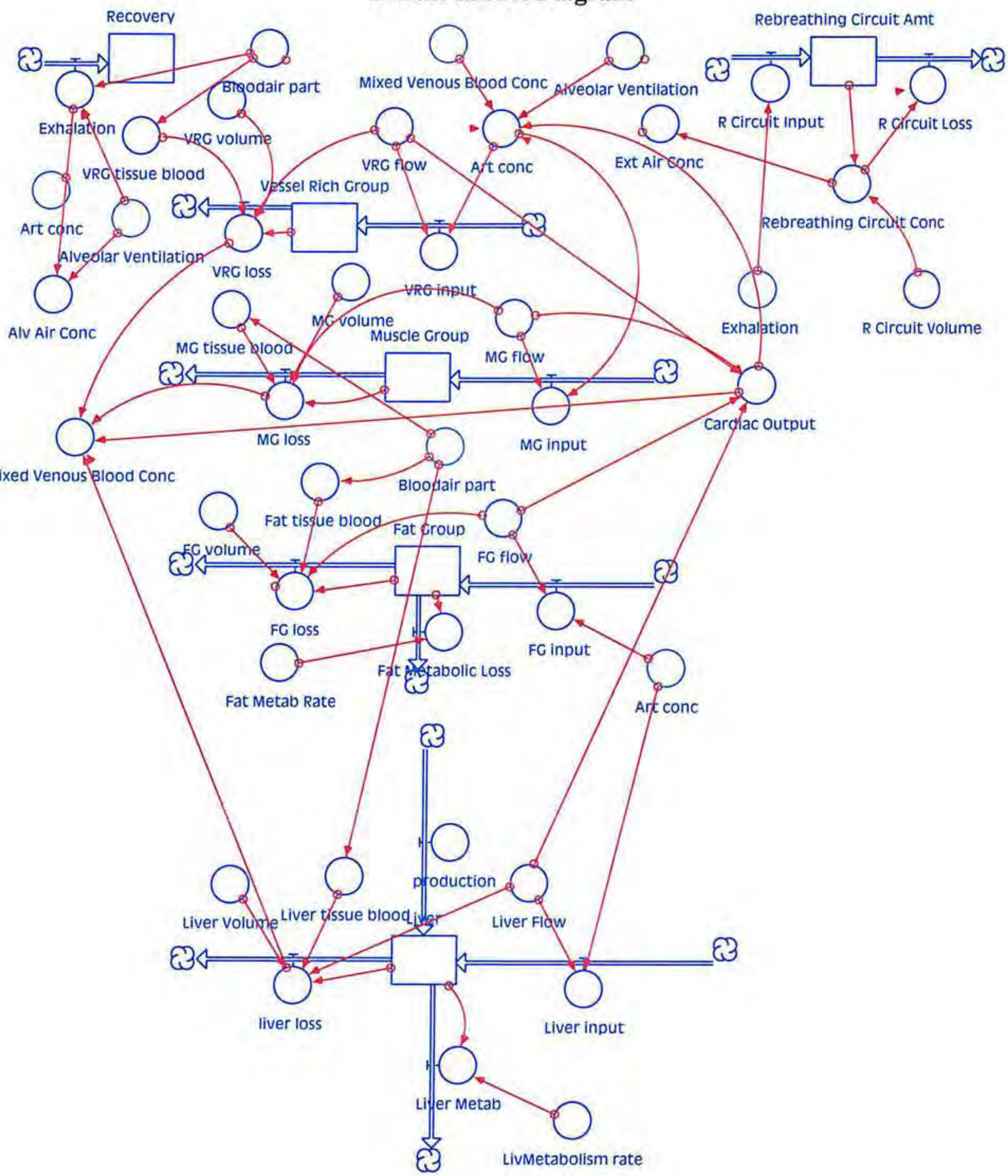


Table 8
Ethane Model Equations

Equations Describing the Inputs and Outputs from Compartments (Boxes in the Model Diagram):

Fat_Group(t) = Fat_Group(t - dt) + (FG_input - FG_loss) * dt
INIT Fat_Group = 20000

FG_input = Art_conc*FG_flow
FG_loss = Fat_Group*FG_flow/(FG_volume*Fat_tissue_blood){Place right hand side of equation here...}

Liver(t) = Liver(t - dt) + (Liver_input + production - liver_loss - Liver_Metab) * dt
INIT Liver = 60.34{Place initial value here...}

Liver_input = Art_conc*Liver_Flow{moles/min}
production = 80 {80 pmol/min estimated for an 80 kg man acording to Habib data; 111 pmol/min would be predicted from Wade and Van Rij central estimate of 95.1 ± 19 pmol/hr-kg for a 70 kg modeled person }
liver_loss = Liver*Liver_Flow/(Liver_Volume*Liver_tissue_blood){ moles/min}
Liver_Metab = Liver*LivMetabolism_rate {Place right hand side of equation here...}

Muscle_Group(t) = Muscle_Group(t - dt) + (MG_input - MG_loss) * dt
INIT Muscle_Group = 655{Place initial value here...}

MG_input = Art_conc*MG_flow{ Place right hand side of equation here...}
MG_loss = Muscle_Group*MG_flow/(MG_tissue_blood*MG_volume) {Moles/min}

Rebreathing_Circuit_Amt(t) = Rebreathing_Circuit_Amt(t - dt) + (R_Circuit_Input - R_Circuit_Loss) * dt
INIT Rebreathing_Circuit_Amt = 0{pmoles}

R_Circuit_Input = if (time<1090) then 0 else Exhalation {pmoles/min}
R_Circuit_Loss = if (Time<1090) then 0 else Alveolar_Ventilation*Rebreathing_Circuit_Conc

Recovery(t) = Recovery(t - dt) + (Exhalation) * dt
INIT Recovery = 0

Exhalation = Alveolar_Ventilation*Art_conc/Bloodair_part{moles/min}

Vessel_Rich_Group(t) = Vessel_Rich_Group(t - dt) + (VRG_input - VRG_loss) * dt
INIT Vessel_Rich_Group = 66.92{Place initial value here...}

VRG_input = Art_conc*VRG_flow{moles/min}

VRG_loss =
Vessel_Rich_Group*VRG_flow/(VRG_volume*VRG_tissue_blood){moles/min}

Equations for Parameters (Circles in the Model Diagram)

Alveolar_Ventilation = 7 {liters/min}

Alv_Air_Conc = Exhalation/Alveolar_Ventilation{pmol/liter}

Art_conc = Bloodair_part*(Cardiac_Output*Mixed_Venous_Blood_Conc+Ext_Air_Conc*
Alveolar_Ventilation)/(Cardiac_Output*Bloodair_part+Alveolar_Ventilation) {pmoles/liter}

Bloodair_part = .105

Cardiac_Output = FG_flow+Liver_Flow+MG_flow+VRG_flow{liters/min}

Ext_Air_Conc = If (Time<1000) then 374 else 0*Rebreathing_Circuit_Conc
{Rebreathing_Circuit_Conc 374 pmoles/liter atmospheric background? 6.64 pmol/l in hydrocarbon free air according to Habib data}

Fat_tissue_blood = 2.7/Bloodair_part

FG_flow = .34{liters/min}

FG_volume = 15.024 {liters}

Liver_Flow = 1.34{liters/min}

Liver_tissue_blood = .05/Bloodair_part

Liver_Volume = 2.476{liters}

LivMetabolism_rate = 0.3

MG_flow = 1.5{liters/min}

MG_tissue_blood = .05/Bloodair_part

MG_volume = 34.756 {liters}

Mixed_Venous_Blood_Conc =
(FG_loss+liver_loss+MG_loss+VRG_loss)/Cardiac_Output{moles/liter}

Rebreathing_Circuit_Conc = Rebreathing_Circuit_Amt/R_Circuit_Volume{pmoles/liter}

R_Circuit_Volume = 14{liters}

VRG_flow = 3.38 {liters/min}

VRG_tissue_blood = .05/Bloodair_part}

VRG_volume = 3.551{liters}

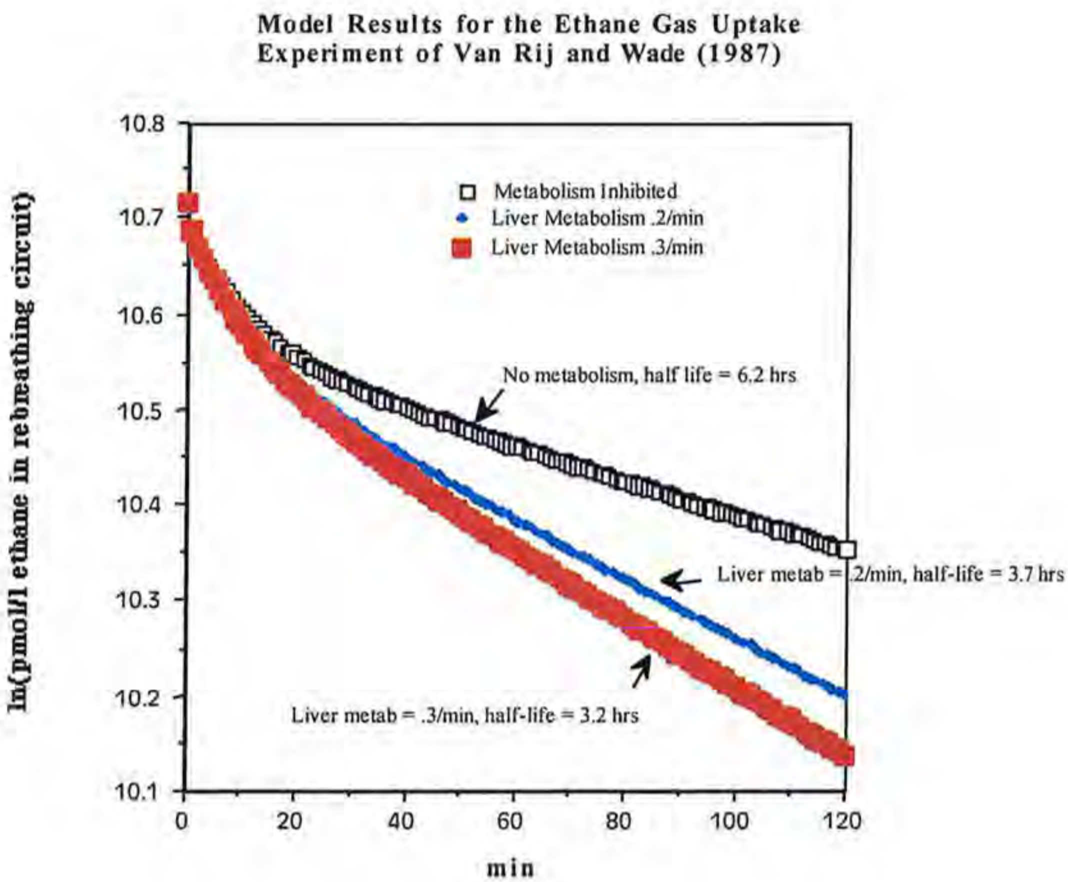
would yield a model in which the rebreathing circuit concentration would decline with an elimination half-life without metabolism corresponding to the observed value of 6.2 hours. This resulted in the following estimates for the various tissue/blood partition coefficients:

Tissue	Tissue/blood partition coefficient
Fat	25.7
Muscle, Liver, VRG	0.48

Based on this, we then tuned the liver metabolism rate to .2 to .3/min (giving half lives of 3.7 and 3.2 hours, respectively in comparison to the target value of 3. 6 hours). Plots of these results in a form comparable to Figure 1 of the Van Rij and Wade(1987) paper's are shown in Figure 5. The overall pattern of the model decline is similar to the original data.

We can also compare the model expectations for the accumulation of ethane in the rebreathing system with the actual observations. To do so, however, we need to confront the one of the central questions we posed at the beginning of this section--how much is the ethane "production" measured in these experiments likely to include ethane absorbed from the external environment, stored in the fat, and then released slowly into the expired air?

Figure 5



This clearly requires some information or an assumption about how much ambient ethane the Wade and Van Rij (and Habib/Do) subjects were exposed to over the day or two prior to the measurements. Unfortunately neither group provides this information. Failing this, we have drawn on data of Shah and Heyerdahl (1988) as quoted in the on-line Hazardous Substances Data Base. Based on 571 measurements, this source reports an urban average ethane concentration of 9.15 ppb by volume, which translates into 374 pmoles/liter at 25^{0} C.

Table 9 shows the basic results of exercising the model to make comparisons with the Van Rij and Wade (1987) observations of the end concentration of ethane in their rebreathing system after (1) a 90 minute period of "washout" with air containing no ethane and then (2) a 120 minute period of connection with the rebreathing system (in which the "external air concentration" in the model is set equal to the continually increasing rebreathing system concentration). The Van Rij and Wade (1987) observations are given in the last column; the model "predictions" for the end concentration in the rebreathing system are given in the second to the last column for various combinations of the parameters shown in the earlier columns.

The first two lines of Table 9 reflect our base assumptions--the ethane production rate reported by the authors, and the typical urban external air concentration we have imported from other data. It can be seen that under these base conditions, the model predicts ethane concentrations in the rebreathing system that are somewhat higher (by 28-58%) than those observed

Table 9
Model Comparisons with the End Concentrations of Ethane in the Wade and Van Rij Rebreathing System Experiments

External Air Conc. (pmoles/l)	Liver Metabolism Rate (per min)	Ethane Production Rate (pmol/min)	Fat Group Flow (l/min)	Fat Group Storage Prior to Washout (nmoles)	Modeled End Conc. in Rebreathing System (pmoles/l)	Reported End Conc. in Rebreathing System (pmoles/l)
374	0.3	111	0.34	15.6	584	370
374	0	111	0.34	15.8	799	622
374	0.3	111	0	15.6	582	370
374	0	111	0	15.8	819	622
100	0.3	111	0.34	4.5	534	370
100	0	111	0.34	4.7	744	622
100	0.3	80	0.34	4.4	390	370
100	0	80	0.34	4.5	541	622
374	**0.3**	**80**	**0.34**	**15.5**	**440**	**370**
374	**0**	**80**	**0.34**	**15.6**	**597**	**622**

The third and fourth lines indicate that the problem is not with excessive release of stored ethane from the fat. Even though the predicted fat store is substantial (third column--over 15 nmoles = 15,000 pmoles), cutting off the blood flow to and from the fat compartment does not materially change the net output reflected in the end-rebreathing concentration. The opposite signs of the effect of cutting off blood flow in the two cases reflect the fact that in the normal case (when blood is flowing through the fat) the fat plays two different roles in the context of the rebreathing system--at early times after the connection is made, the fat makes a net positive contribution to ethane output; however toward the end of the two hour period the fat is actually absorbing more of the generated ethane than it is releasing when the external air concentration rises above the 300+ pmole/liter air concentration with which it is equilibrated. The intrinsic half-life for the release of ethane from the fat compartment is $\frac{\ln(2)}{\text{fat flow/(fat volume * fat tissue/blood)}} = 13$ hours so it is not possible to eliminate the ethane from the fat compartment with any feasible washout procedure. The fat contribution can be estimated however, based on estimates of the background air concentration and simple measurements of body composition. Later we will exercise the model to develop preliminary formulae for this correction as a function of washout time.

The fifth and sixth lines of Table 9 show what happens to the model projections when the external air concentration assumed for pre-equilibration is lowered to 100 pmoles/liter. It can be seen that this leads to a major reduction in the accumulated fat store, but not a large enough reduction in the air output to the rebreathing system to reconcile the results with the observations of Van Rij and Wade (1987). The differential is due to the fact that in part because of the 90 minute washout period, the rate of production of ethane has a much stronger influence on the output to the rebreathing system than the release from the fat stores [compare with the results in the seventh through tenth lines of the table, which reflect a modest (28%) reduction in the production from 111 pmole/minute (equivalent to Van Rij and Wade's estimate of 95.1 pmoles/kg-hr) to 80 pmole/minute]. The final (9th and 10th) lines of the table reflect our best judgment of the set of parameters that is most compatible with all our available information. This form of the model will be used to make tentative inferences about the effects of various washout periods, background ethane exposures, and body fat content on alveolar ethane concentration measurements as done by Habib et al. (1995).

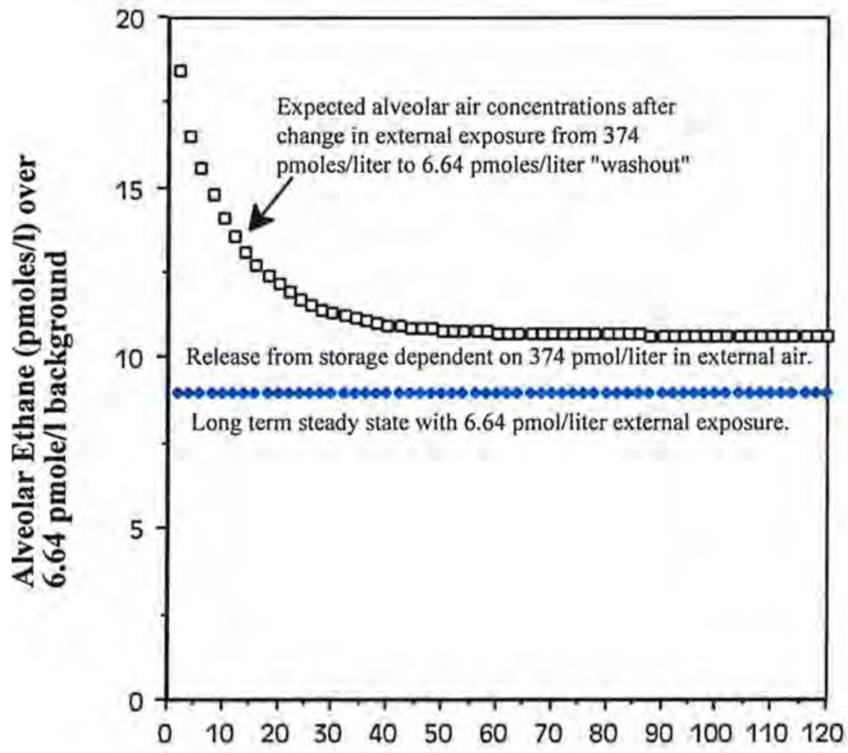
Use of the Ethane Model to Assess the Influence of Various Factors on Ethane Exhalation, and Interpretation of Ethane Measurements In Terms of Internal Ethane Production

Figure 6 shows the results of using our model to simulate the fall of alveolar ethane concentrations during "washout" as specified by Habib et al. (1995), assuming prior equilibration with 374 pmoles/liter in external air and 80 pmoles/minute true production. It can be seen that a few minutes of washout as described by these authors cannot be expected to be sufficient to achieve good stability in the excretion of ethane originating from "background" sources. 40-90 minutes of "washout" seems desirable. After attainment of a full steady state, the model predicts an excess exhalation of 8.98 pmoles/liter in alveolar air over and above the 6.64 pmole/liter background in the low hydrocarbon air used by Habib et al. Because the model assumption is for an alveolar exhalation rate of 7 liters per minute, this means a net excreted ethane production of 62.9 pmoles/minute. (This is less than the 80 pmoles/min production rate built in to the model because some of the ethane produced is metabolized before it has a chance to be exhaled.) Table

10 shows the decline in excess exhalation of ethane from body stores over this background at various times after the start of "washout".

Figure 6

Model Expected Alveolar Exhalation Over Background During "Washout"



The data in Table 10 allow a relatively simple correction to be made to observed ethane alveolar exhalation data for prior steady state exposures to ethane in external air. Because the model is completely linear, the expected excesses due to stored ethane form external air exposures other than 374 pmoles/liter should simply be adjusted upward or downward in proportion to the actual average external background exposure level for the previous day or so.

It is also of interest, of course, to assess how this correction should be changed in relation to body build/fat content. There is some ambiguity in exactly how one should adjust the model for a larger fat compartment. One can, of course, simply increase the fat volume parameter in the model, but it is not completely clear whether or how one should make corresponding adjustments in the blood flow rate to the fat tissue. For our preliminary purposes here we have elected to bound the problem with two extreme cases: (1) an assumption that the fat flow increases in parallel with the fat volume, keeping the flow/volume ratio (and hence the half life of loss from the fat tissue) constant; and (2) an assumption that fat flow is unchanged even as fat volume increases. Using both assumptions we tested the effect of a doubling of fat flow.

Table 10
Expected Decline of "Excess" Alveolar Exhalation from Body Stores During Various Periods of Washout

Minutes after start of washout	Excess alveolar conc over steady state resulting from stored ethane	pmoles/min excess excretion dependent on release of stored ethane
2	9.46	66.22
4	7.55	52.85
10	5.16	36.12
20	3.19	22.33
30	2.36	16.52
40	2.02	14.14
50	1.86	13.02
60	1.79	12.53
70	1.75	12.25
80	1.73	12.11
90	1.71	11.97
100	1.69	11.83

Table 11
Effect of Doubling The Size of the Fat Group (From About 15 liters to 30 liters) on the Expected Decline of "Excess" Alveolar Exhalation from Body Stores During Various Periods of Washout

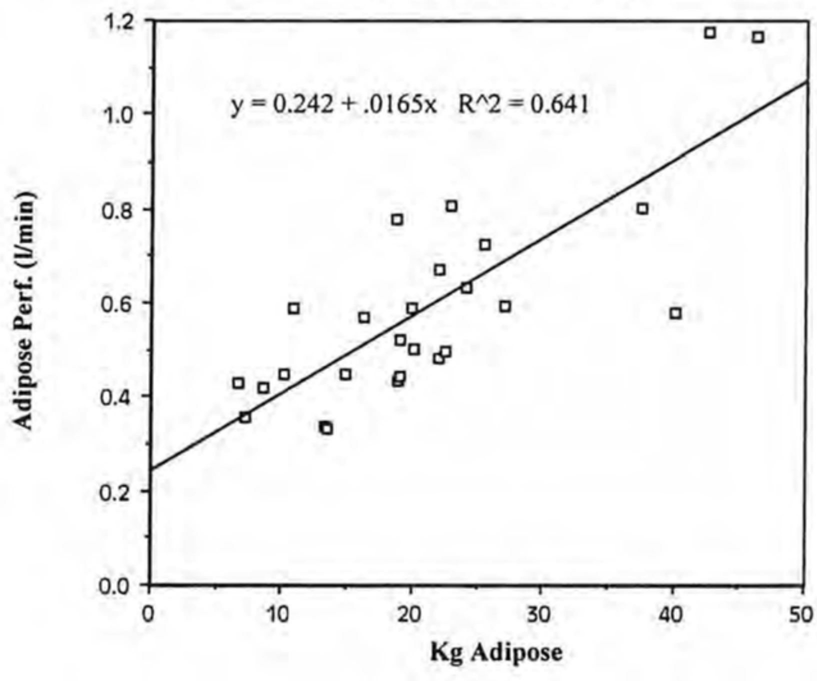
	Double FG Volume and Flow		Double FG Volume Only	
Minutes after start of washout	Excess alveolar conc over steady state resulting from stored ethane	pmoles/min excess excretion dependent on release of stored ethane	Excess alveolar conc over steady state resulting from stored ethane	pmoles/min excess excretion dependent on release of stored ethane
2	11.19	78.33	9.45	66.15
4	9.3	65.1	7.55	52.85
10	6.93	48.51	5.17	36.19
20	4.95	34.65	3.2	22.4
30	4.12	28.84	2.38	16.66
40	3.76	26.32	2.04	14.28
50	3.6	25.2	1.9	13.3
60	3.51	24.57	1.83	12.81
70	3.46	24.22	1.8	12.6
80	3.42	23.94	1.79	12.53
90	3.39	23.73	1.77	12.39
100	3.36	23.52	1.76	12.32

The results are shown in Table 11 in parallel to the format of Table 10. Comparing the results in the two tables, it can be seen that the effect of simply doubling the fat volume (Case #2) is minimal. On the other hand, if the fat group flow is also doubled, then the increment to excess alveolar concentration over steady state at long times after the start of washout is also approximately doubled.

Some guidance on which of these is closer to the truth can be gleaned from recent studies of Pierce et al. (1996) for toluene. In an excellent series of clinical pharmacokinetic experiments on 26 people with a defined exposure and extensive post-exposure follow-up, Pierce et al. developed individual estimates of several key pharmacokinetic parameters, including the blood flow through the fat tissue. The relationship between estimated fat blood flow and measured adipose tissue volume is shown in Figure 7. These data indicate that fat blood flow does tend to increase with the size of the fat compartment, but not quite proportionally as assumed in our "case 2". The relationship shown in Figure 7 allows a better basis for developing the needed correction factors for the excretion of stored ethane.

Figure 7

Observed Relationship Between Adipose Tissue Volume and Adipose Perfusion in Humans Exposed to Toluene--Data of Pierce et al (1996)



In conclusion, it does seem that it is feasible to measure ethane production in humans with the aid of alveolar air samples taken ideally with a substantial (40-90 minute) period of washout. The accuracy of such measurements can be enhanced by pharmacokinetic model-based corrections, taking into account (1) body fat content and (2) measurements or estimates of the concentration of ethane in ambient air breathed in by the subject in the day prior to the breath measurements.

Development of a Physiologically-Based Pharmacokinetic Model for Pentane
Work is currently under way to apply the same analytical approach to development of a PBPK model for pentane. Initially, we have chosen to use the complete set of blood/air and tissue blood partition coefficients given by Perbellini et al. (1983) (see Table 6, above). The pentane production rate is being tuned to produce the rebreathing system concentration seen by Van Rij and Wade (1987) with inhibition of metabolism (1600 pmoles/liter). Then the metabolism rate will be tuned to reduce output sufficiently to reduce the model "predicted" rebreathing system concentration to the 120 pmoles/liter reported by Van Rij and Wade(1987).

Even before completion of this modeling it is clear that fat storage of pentane taken in from the ambient air is likely to be a significant factor that will need to be taken into account in interpreting any pentane breath measurements in terms of internal pentane production. Given the estimated fat/blood partition coefficient for pentane of 104, the indicated half-life for loss of pentane from fat is expected to be about 53 hours--about four times longer than the corresponding figure for ethane. Measurements of pentane air levels in urban areas range widely and may be complicated by the same sort of measurement difficulties (e.g., interference from isoprene) as have caused such confusion with respect to breath samples. Initial modeling is being done based on the 134 pmoles/liter reported by Kohlmuller and Kochen (1993).

Conclusions--recommended procedures for study of these parameters in populations exposed to putative lung-damaging agents, and in ex-workers previously exposed.

What screening/control questions need to be asked in order to adequately control for confounders?

For alkane exhalation it is clearly necessary to make measurements or estimates of body fat content, and to ascertain whether the subject is a smoker. It may also be helpful, but probably not absolutely necessary to measure vitamin E levels in serum.

For urinary desmosine/isodesmosine measurements there should be some consideration to asking the subject about dietary habits--and in particular the consumption of meats with a high content of cartilage. The findings of relatively modest (statistically not significant) excess desmosine/isodesmosine urinary output suggest that these measurements will not usually be seriously affected by meat-eating habits, but some further inquiry in this regard seems prudent. Whether spot urine samples are used or 24-hour collections are made, the results must be corrected for creatinine excretion. This may have the effect of reducing whatever meat-consumption effect there may be on these parameters.

Finally, smoking and occupational history information should also be collected for studies of all biomarkers of putative lung damaging agents.

Based on an analysis of the pharmacokinetic/pharmacodynamic information, what experimental precautions need to be taken (e.g., washout, repeated measures) in order to produce high quality data?

Three basic suggestions have emerged from the prior analysis:

1) For both ethane and pentane, there needs to be a small series of measurements of pharmacokinetic parameters both in vitro (e.g., ethane blood/air, liver/air, and related partition coefficients) and in vivo (based on measured exposures) to confirm the pharmacokinetic modeling outlined earlier. These models will be an important part of assuring that breath observations can be corrected for the release of alkanes stored as the result of exposures to the same materials in ambient air.

2) Improved ethane (and/or pentane) ambient air measurements need to be made covering the day or two prior to breath measurements for at least a sample of study subjects.

3) Characterization of individual rates of excretion of desmosine and isodesmosine may benefit from a small series of repeated samples, spaced apart by at least a couple of weeks. Group differences, however, may well be detected by cross-sectional samples in which only a single measurement is made per person.

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Dr. Shane Que Hee and colleagues

1. Three papers have been published/accepted (1,2) or submitted (3). One has been published from the Master of Science thesis of Soo Young Kim (1), and another accepted from the work of doctoral students Yang Shen and Ju-Chien Tso (2). The third has been submitted from the Master of Science thesis of Keummi Park (3). (Appendix B)

The major achievement was the optimization (efficiency >80%; imprecision <10%) of the cordless microvacuum method for sampling dust of <180 μm particle size that contains xenobiotics. The latter included metallic species like metal oxides (1,4), a formulation of the reference pesticide chlorpyrifos (2) and Rhodamine 6G dye (2)) and a freeze-dried microbe (*Photobacterium phosphoreum*) (3). The optimized method utilized a flow rate of 4.0 L/min and multiple sampling passes of the sampling probe over a known area defined by a sampling template containing >15 mg/100 cm^2 up to at least 170 mg/100 cm^2. The sampling technique for total dust was based on a microsampling technique originally reported by Que Hee et al in 1985 (4) for available dust in lead abatement and lead surface sampling activities.

The initial study (1) investigated the effect of particle size, surface coverage, surface type, flow rate, number of sampling passes, sampling technique, sampling face velocity, and degree of training on soil sampling efficiency from relatively flat hard surfaces, using the low flow technique (4) at 1.5 L/min as the starting point. The sampling apparatus was the same as the portable personal sampling pump/filter cassette combination that is standard for air sampling of aerosols by industrial hygienists, with the addition of a 5.0 cm x 0.6 cm ID Tygon sampling probe whose sampling end was cut at a 45^o angle. Minimum soil holdup on the sampling apparatus surfaces allowed low soil surface coverages to be sampled efficiently. Soil was used since the Santa Ana wind from the desert causes much infiltration of Los Angeles homes, and soil is imported into homes by shoes. Efficient sampling (efficiency ≥87%; coefficient of variation (CV) <5%) of dry, loose soil on a 100 cm^2 template was achieved between coverages of 10 mg/100 cm^2 and 170 mg/100 cm^2 using at least 3 sampling passes for particle sizes between 63 μm and 180 μm. The technique was efficient because the face velocity developed at the surface was as high as 1083 ft/min for a 1 mm^2 surface-to-probe space.

The second paper (2) is the accepted paper demonstrating that spilled Rhodamine 6G dye and a NIST dust and a NIST soil impregnated with a chlorpyrifos formulation at its expected maximum coverage will also be sampled efficiently and precisely by the technique developed in Appendix B. Rhodamine 6G is used at Los Alamos National Laboratory as a fluorescent dye in tunable dye lasers. Powder is often spilled preparing the solutions, and a dry deposit occurs after a spill of solution. Spilled powder tends to cake since it is slightly hygroscopic, and thus is difficult to sample since it tends to cling to the surface. The flow rate had to be ≥3.0 L/min to provide quantitative sampling recovery on the first sampling pass. Below 2.0 L/min, all of the sample resided in the sampling probe and did not reach the filter cassette at all. As the flow rate increased more sample was retained on the filter. The weight of the entire sampling ensemble requires measurement, not the filter portion alone. The mass collected on the filter is only likely to be representative of the spill at the highest sampling flow rate of 4.0 L/min.

Chlorpyrifos, an organophosphorothioate pesticide, has been measured at concentrations up to 1300 mg/kg dust, and surface coverages up to 990 μg/m^2. The EPA in 2000 banned application of chlorpyrifos within dwellings where children could be exposed. The hypothesis relative to sampling efficiency was that the pesticide of highest concentration in dust was most likely to decrease the sampling collection efficiency of uncontaminated dust using the optimized 3-pass methodology at 4.0 L/min. Thus the experiment involved comparison of coated and uncoated dust. NIST SRM 2711 Montana Soil of <74 μm particle size, and SRM 1649a Urban Dust of <125 μm particle size were coated with Lorsban 2E formulation. The latter consisted of 40.7% chlorpyrifos, and 59.3% inert ingredients, mostly alkylbenzenes, as demonstrated through GC/MS analysis of the formulation. 31.94 mg in acetonitrile was coated onto 10 g of dust or soil to simulate the highest measured dust concentration of 1300 mg/kg. Loadings of 10-20 mg of impregnated soil and dust at 1300 mg/kg concentration were investigated relative to uncoated dust and soil on the 100 cm^2 template surface using the 3-sampling pass technique developed in Appendix B. The lower surface coverage range for efficiencies >79% and imprecisions <16%

CV was 15-20 mg/100 cm^2 for both coated and uncoated dust or soil, with lower efficiencies being evident for coated soil and uncoated dust. The lower efficiencies for coated soil were caused by enhanced particle agglomeration and increased stickiness; this cannot explain the contrary results for coated dust. For the latter, the initial particle size was bigger than for the soil, and particle sizes between 63 μm to 180 μm cause no difference in sampling efficiency.

The third paper currently under review (3) presents the research associated with sampling spills of the freeze-dried bacterium, *Photobacterium phosphoreum*. The major finding relative to sampling spilled powder was that since freeze-dried bacteria was a very deliquescent powder the cassette entry port inner diameter had to be increased to accommodate large chunks to achieve sampling efficiences >80%. Once the material becomes too damp, swabs with handles are the best way to sample/clean up spills. During this investigation, the Microtox test of viability based on bioluminescence was compared with a commercial colorimetric test to assess the effect of dust on bacterial viability. The addition of 20 mg of NIST 1649a urban dust per mL caused complete inhibition of the Microtox test as did 5 mg of dust for the colorimetric test. Complete desiccation caused bacterial death in both tests. The major problem with the colorimetric test using the naked eye was its insensitivity; sensitivity was improved twofold by developing a spectrophotometric technique at 508 nm, and this rivalled the sensitivity of the Microtox test. Microtox test results were only completely reliable for homogeneous solutions that passed a 0.45 μm filter.

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American Industrial Hygiene Conference And Exposition (Aihce) Presentations

1. SY Kim, SS Que Hee, JR Froines. Optimized portable cordless vacuum method for sampling dry, hard surfaces. AIHCE, May 17-23, 1997, Dallas, TX. Abstract 144.
2. Y Shen, SS Que Hee, JR Froines. A surface sampling portable cordless vacuum method for Rhodamine 6G. AIHCE, May 20-25, 2000. Orlando, FL. Abstract 340.
3. JC Tso, SS Que Hee, JR Froines. Surface sampling for soil impregnated with chloropyrifos formulation. AIHCE, Orlando, FL, 2000. Abstract 328.

Master Of Science Theses

1. Soo Young Kim. Optimized portable cordless vacuum method for sampling dry, hard surfaces for dusts, 1997.
2. Keummi Park. Microtox test as a validation method for surface sampling of bacteria in dust, 1999.

4. Integrated task and postural analysis for ergonomic exposure analysis. To develop, pilot test,and validate an integrated task and postural analysis for ergonomics exposure assessment

Wen Chen V. Liu, Ph.D., CIH, CSP

Hazard Surveillance in the Defense/Nuclear Industry - Occupational Ergonomics Component - Overview

The Occupational Ergonomics component of this research project contains five subprojects. The first two subprojects focused on the development of exposure and response surveillance tools to be used through Internet as a means for ergonomic hazard surveillance in the office work environment using visual display terminals. The third and the fourth studies focused on the evaluation of ergonomic hazards in a defense/nuclear facility that utilizes glovebox and Hypalon glovebox gloves. The fifth subproject focused on the development of a real-time heat stress-heat strain personal monitor for workers wearing total encapsulated protective suits, as heat stress has been indicated as one of the major hazards encountered by many workers in the defense / nuclear industry are involved in the decommission and decontamination activities. The title, significant findings, usefulness of the findings, and dissemination of the findings of each of the subproject are briefly summarized as follows.

Subprojects:

I. Computer Usage and Upper Extremity Musculoskeletal Discomfort in an Engineering Firm of the Aerospace/Defense Industry - A Survey through Intranet.

Significant Findings

This study represents the first electronic survey through Intranet that evaluated the association between self-perceived computer usage and self-reported musculoskeletal discomfort of the upper extremity. In addition, the population studied included engineers in an Aerospace/Defense Industry, a profession that has not been studied in terms of the prevalence of self-reported musculoskeletal discomfort. Furthermore, the survey was conducted electronically the company's Intranet. Nine hundred and ninety-seven employees (277 females and 717 males) of the company responded to the survey in two weeks. The results of logistic regression analysis indicated that gender, job tenure, and hours of computer usage were three factors significantly associated with the prevalence of musculoskeletal discomfort in the upper extremity.

Usefulness of the Findings

This study demonstrated that Intranet and Internet is an expedient and useful tool for the surveillance ergonomic hazards in office work environment.

Dissemination of the Findings

An abstract of the results of the study was presented at the 1999 American Industrial Hygiene Conference and Exhibition. A manuscript based on the study is being reviewed for consideration for publication in a peer-reviewed journal (Applied Occupational and Environmental Hygiene).

II. A Software-Based Tool for Exposure Assessment of VDT Work through Internet.

Significant Findings

An innovative software-based exposure surveillance tool was developed in this subproject to objectively quantify office workers' usage of computer input devices. This software-based tool would replace subjective estimate of exposure to biomechanical factors associated with the development of computer input device-related musculoskeletal disorders/discomfort.

Usefulness of the Findings

In this project we created a software-based exposure surveillance tool that can objectively quantify office workers' usage of computer input devices. The results of the study were also incorporated in another research proposal funded by the NIOSH under the NORA initiative for field evaluation.

Dissemination of the Findings

An abstract of the results of the study was presented at the 1999 American Industrial Hygiene Conference and Exhibition. A manuscript based on the study is being revised for consideration for publication in a peer-reviewed journal (American Industrial Hygiene Journal).

III. Hazards in Glovebox Operations in a Defense/Nuclear Facility - Through Ergonomic Task Analysis.

Significant Findings

Two ergonomic task analyses were conducted for two glovebox operations in a Defense/Nuclear Facility. The first ergonomic task analysis was conducted for an operation that casts metal inside a glovebox. The specific aim of this analysis was to identify opportunities for continuous improvement in terms of reducing musculoskeletal load. The ergonomic task analysis, consisting of task analysis, postural analysis, and static strength modeling, was applied to two on-site simulations and to actual casting operation recorded on videotape. The results of the postural analysis indicate that the work environment and the tasks involved in casting operation do occasionally place the operators in awkward posture. As a result, the working conditions should be modified sometime soon. The results of static strength modeling show that several tasks involving lifting heavy molds are not designed for the majority of the general population. These tasks could be modified by rearranging the internal layout of the glovebox and by installing auxiliary material handling devices in the glovebox.

The second ergonomic task analysis was conducted of an operation that refines metal in specific forms. This particular glovebox operation has experienced high frequency of abnormal glove breaches. The specific aim of the analysis was to identify improvements that could reduce the incidence of glovebox glove failures. Document reviews, individual interviews, small group meetings, and on-site observations were conducted during the investigation. The results indicate that there are many micro and macro ergonomic improvements that could be made to increase the reliability of the glovebox gloves and the comfort of the workers.

Usefulness of the Findings

This case study demonstrated the utility of a systemic approach that addresses both macroergonomic and microergonomic issues in improving the health and safety of workers in a Defense / Nuclear facility. A portion of the study was also used to demonstrate the Defense / Nuclear facility's effort and achievement under the Price-Anderson Act regulating the facility.

Dissemination of the Findings

A case study was presented by a collaborator of the study at the 1998 American Industrial Hygiene Conference and Exhibition. A manuscript is being revised for submission for consideration of publication in a peer-reviewed journal (Industrial Health).

IV. Validation of an Experimental Device for the Measurement of Kinetic Friction.

Significant Findings

An experimental device was developed in this project for the measurement of kinetic coefficient of friction. In addition, the kinetic coefficient of friction (μ_k) of fingertip was measured for six Chinese subjects on textured and non-textured surfaces in this exploratory study. The results indicate that μ_k of the fingertip skin varies with the magnitude of normal force and the surface texture of the test plates. The μ_k decreased as the exerted normal force increased. The highest value of μ_k was 2.05 for males and 2.26 for females with 1 N normal force on a test plate of 100% contact area. When the load increased to 10 N, μ_k decreased to 1.09 for males and 1.11 for females on the same test plate. The μ_k increased as the contact area increased. For males, there was a 39% and 64% increase, respectively in μ_k as the contact area increased from 50% to 75% and 100%. For female, there were, respectively, a 41% and a 77% increase in μ_k as the contact area increased from 50% to 75% and 100%.

Usefulness of the Findings

Friction is a common mechanical stressor upon human skin. High friction may produce erosions and blisters to human palmar. Friction also affects our ability to manipulate and grasp objects with the hand. Friction between the surface of an object and fingers is also needed for an individual to adjust the amount of force applied in manipulating objects. Low friction objects tend to slip out of the hand resulting in an increase in the potential for injury. Low friction objects therefore require greater grasp forces than objects with high friction. Prolonged, excessive grip forces applied to prevent slippage may cause injuries to tendons and tissues. The experimental device developed in the study has been adopted by a defense / nuclear facility with a robot arm for testing the wearability of glovebox gloves. The results of the study will be used to develop guidelines of glovebox glove design.

Dissemination of the Findings

An abstract of the results of the study was presented at the 1999 American Industrial Hygiene Conference and Exhibition. A manuscript based on the results of the study is being revised for consideration for publication in a peer-reviewed journal (Applied Ergonomics).

V. A Real-Time Personal Heat Stress & Heat Strain Monitor in Protective Suit.

Significant Findings

The goal of this study was to develop a real-time personal monitor capable of evaluating heat stress and heat strain encountered by workers wearing encapsulating protective clothing. This monitor simultaneously characterized the climatic condition of the microenvironment and the physiological responses of the worker in protective clothing. Specifically, the study: (1) integrated temperature and humidity sensors to continuously characterize the microenvironment in a protective suit; (2) integrated heart rate sensors and body temperature sensors to characterize the physiological response of the person wearing a protective suit; and (3) tested the utility of two wireless transmitters, 0.9 GHz and 2.4 GHz, to transmit the heat stress and heat strain signals.

Usefulness of the Findings

This study represents an innovative integration of information technology and sensor technology for hazard surveillance. In addition, this study has direct application to personal exposure surveillance of workers wearing protective suits and utility for the design of protective clothing.

Dissemination of the Findings

An abstract of the preliminary results of the study has been submitted for presentation at the 2000 American Industrial Hygiene Conference and Exhibition. Manuscript is being revised according to reviewers' comments for publication in a peer-reviewed journal (Applied Occupational and Environmental Hygiene Journal).

Wen Chen V. Liu, Ph.D., CIH, CSP and Craig Conlon, MD

Computer Usage and Upper Extremity Musculoskeletal Discomfort in an Engineering Firm of the Aerospace/Defense Industry - A Survey through Intranet – Subproject I

Abstract

This paper presents the results of a survey that evaluated the association between computer usage and musculoskeletal discomfort of the upper extremity in an engineering firm. The survey was conducted electronically by the firm's ergonomic team through the company's Intranet. Nine hundred and ninety-seven employees (277 females and 717 males) of the company responded to the survey in two weeks. Job functions of the respondents included management (10%), administration (13%), engineering (54%), and others (23%). On the average, the respondents spent more than five hours a day on their computers. Female employees appeared to work with the computers more than male employees do with the computer, 6 hours/day vs. 4.9 hours/day. Forty-seven percent of the respondents reported that they had experienced upper extremity musculoskeletal discomfort 1 month before and at the time of the survey. However, respondents in administrative and "other" job functions seemed to be more likely to experience musculoskeletal discomfort than respondents in engineering and management positions did. Experience of musculoskeletal discomfort in the upper extremity was evaluated using a logistic regression model. The results of logistic regression analysis indicated that gender, job tenure, and hours of computer usage were three factors significantly associated with the prevalence of musculoskeletal discomfort in the upper extremity.

Keywords: Musculoskeletal Discomfort, Engineering Firm, Intranet

Introduction

The use of personal computer in the office environment has been linked to the development of musculoskeletal discomfort/disorders among workers. Bergqvist (1984) and Hunting et al. (1983) demonstrated that visual display terminal (VDT) operators are prone to report musculoskeletal discomfort in the shoulder and in the neck. Kukkonen et al. (1983) have also shown the data entry operators are likely to experience musculoskeletal discomfort in the neck. These studies all focused on workers in jobs characterized by continuous, intensive keying. Other types of office workers, such as engineers and managers, have thus far received relatively little attention in terms of their usage of computers and their experience of musculoskeletal discomfort in the upper extremity.

In this paper, we present the results of a pilot study conducted by an ergonomics team of an engineering firm. This engineering firm has been in operation for more than thirty-five years. At the time of the survey more than four thousand employees were employed. The company had 4000+ personal computers in operation. Some of the employees experienced carpal tunnel syndrome and other musculoskeletal discomfort/disorders believed to be associated with the use of VDT workstation, based on internal medical findings. Together with the firm's Safety and Health staffs, the employees formed an ergonomic team to identify and solve musculoskeletal discomfort some employees were experiencing.

Being an engineering firm with more than two thousand engineers, the ergonomic team had a tremendous amount of resources in terms of computer programming abilities, email and Intranet connectivity. In addition, the management is committed to provide the human resources necessary in initiating a study to identify the prevalence of the musculoskeletal discomfort/disorders problem associated with computer usage. Having received some reference materials regarding the design of a self-reported exposure assessment and discomfort survey, the ergonomic team developed a dynamic webpage and conducted a pilot study.

This pilot study, because of its exploratory nature, had a simple objective. That was to get an estimate of the computer usage among employees and of the prevalence of musculoskeletal discomfort in upper extremity.

Methods

The methods the ergonomics team used to accomplish the above goals was to conduct an exposure and discomfort survey through Intranet. The engineer developed a questionnaire using the HyperText Markup Language. Emails were then sent to managers in the company soliciting the managers' cooperation in forwarding the messages to their groups of employees, including the professionals, clerical staffs, technicians, etc. The emails forwarded to the employees contained a link to the survey webpage on their Intranet. If the employee chose to respond, by a single click on the link, he/she gets onto the questionnaire webpage. Within a two-week period, nine hundred and ninety-seven employees of the company responded to ergonomics team's email request.

Excluding three respondents who did not provide information regarding their gender, there were 277 females and 717 males. Mean age of the male respondents 44.5 (SD=10.4 year) is not significantly greater than the mean age of female respondents, 41.4 year (SD=10.5 year). Mean tenure of the respondents was 9.3 year and the SD was 8.1 year. Male respondents had a mean tenure of 9.8 year (SD=8.5 year), higher than the mean tenure of 9.3 year (SD=8.1 year) of the female respondents ($p < 0.01$). Male respondents were also taller and heavier than female respondents were. For male respondents, the mean stature was 178.7 cm (SD=7.3 cm) and for female respondents the mean stature was 163.6 cm (SD=7.2 cm). For male respondents the mean body weight was 85.2 kg (SD=15.4 kg) and for female respondents the mean body weight was 66.1 kg (SD=14.7 kg).

Questionnaire

The self-administered questionnaire had two sections. The first section collected basic demographic data such as age, height, weight, job tenure, and gender were also collected using the questionnaire.

The second section contained 12 questions. Two questions asked for the number of hours of computer usage and the percentage of which using keyboard, mouse and watching screen. Two questions asked for the frequency of taking breaks away from computer work. One question was regarding the perceived work demand in keying and using mouse. Two questions asked for the dominant hand for writing and for using the mouse. One question asked whether the respondent wore glasses, especially the bifocal or multifocal. One question was on whether the respondent had had his/her workstation evaluated for ergonomic problems. Two questions were asked regarding the specific fingers used in keying and in clicking mouse buttons. One final question asked whether the respondent had experienced any musculoskeletal symptoms in the upper extremity that lasted more than two consecutive days while using the computer. "Musculoskeletal symptoms" were defined as pain/discomfort in neck, shoulder, elbow, forearm, hand; numbness or tingling in arm or hand; and loss of strength.

Data Analysis

Descriptive statistics, chi-square analysis and logistic regression analysis were conducted. Logistic regression was conducted to model the association between the risk factors and the prevalence of upper extremity discomfort observed. Odds ratios were estimated as the antilog of the regression coefficients (Kleinbaum et al. 1982; Hosmer and Lemeshow 1989). A 95% confidence interval was calculated as the antilog of the standard error coefficients multiplied by 1.96 and -1.96. All statistical analysis was conducted with software package SPSS on a personal computer (SPSS 1994). Trend test based on logistic regression was also conducted (Rothman 1986).

Results

Job Function

As shown in Figure 1, 54% of the respondents were engineers and 16% of that were females. 13% of the respondents were administrative staffs and 65% of that were females. 10% of the respondents were managers and 12% of that were females. Respondents with other job titles constituted 23% of the respondents and 40% of which were females. Job titles in the "others" category included: accountants, editors, and drafters.

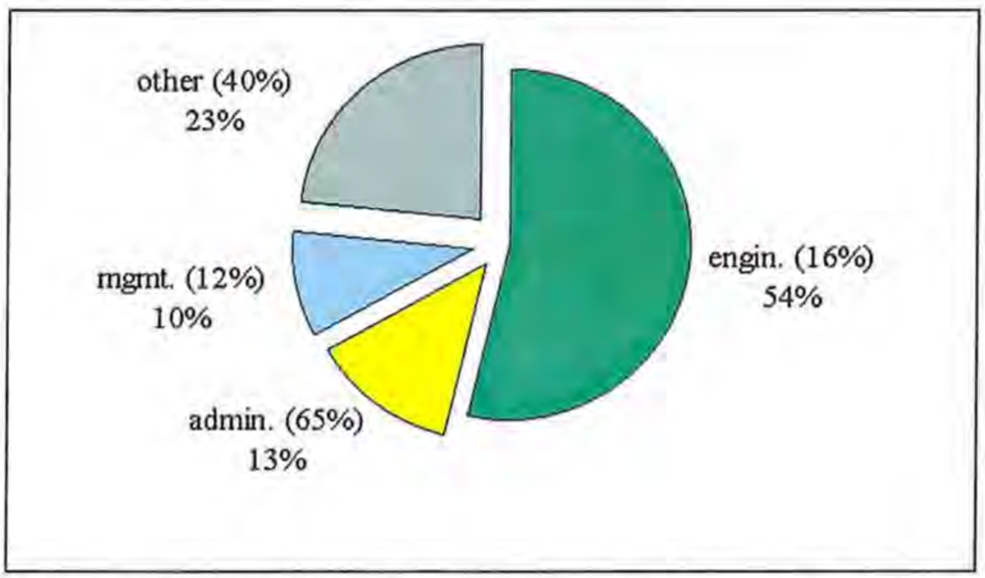

Figure 1. Percentage of participants in four job categories. (% female in each job category)

Computer Usage

Figure 2 graphs self-reported hours of computer usage. Overall, the employees spend 5.2 hours/day on computer. However, female employees seemed to spend more hours each day (mean: 6 hours, SD: 1.7 hours) on computer than male employees did (mean: 4.9 hours, SD: 1.9 hours). The gender difference in the hours of computer usage was statistically significant ($t=8.65$, $p < 0.01$).

Computer usage in this engineering firm also depends on the job functions. As expected, computer usage by the managers (mean: 3.7 hours/day, SD=1.43 hours) was considerably lower than the computer usage (mean: 5.4~5.5 hours/day, SD=1.7~1.9 hours) by respondents of other job functions. The difference in computer usage among respondents of management, engineering, administration, and others was statistically significant ($F=23.6$, $p < 0.01$).

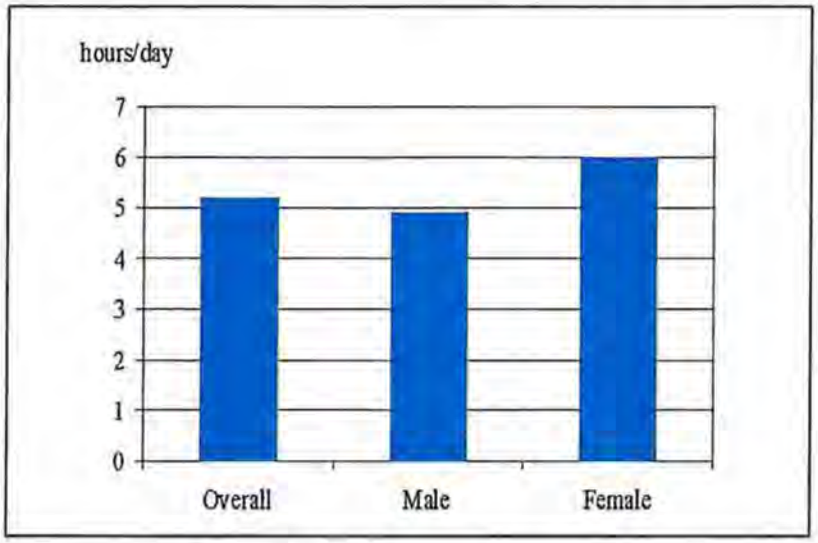

Figure 2. Self-Reported Computer Usage

Prevalence of discomfort by job function.
Figure 3 shows the prevalence of musculoskeletal discomfort in the upper extremity among employees in four job functions. 43% of the engineers and 41% of managers that responded to the questionnaire reported having experienced upper extremities musculoskeletal discomfort, while 56% of the administrative respondents and 52% of the respondents in the job category "Others" reported having experienced musculoskeletal discomfort. Chi-square analysis showed that there was a significant difference in the prevalence of upper extremity discomfort among respondents of these four job functions (Chi-square = 11.0, $p < 0.05$).

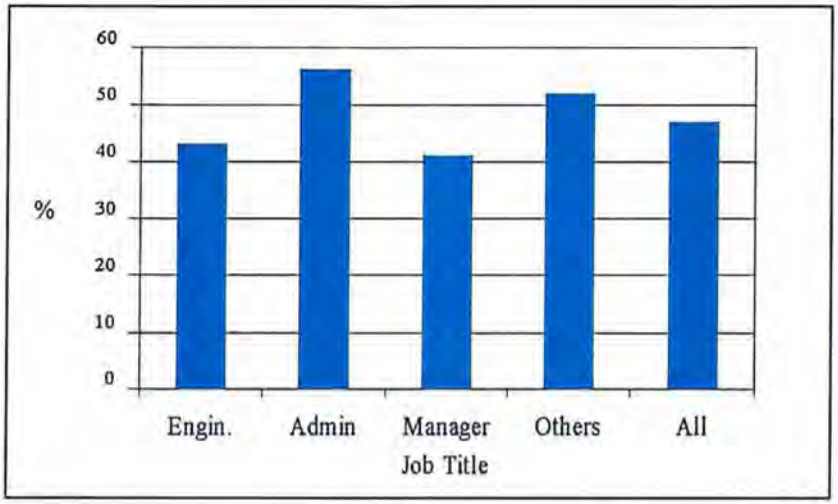

Figure 3. Prevalence of Self-Reported Upper Extremity Discomfort by Job Title

Prevalence of discomfort by tenure group.

Figure 4 shows the prevalence of discomfort by different tenure groups. It seemed that the prevalence of musculoskeletal discomfort increased as the job tenure increased. Overall, the prevalence of discomfort increased from 36.8% for the "less than and equal to 1 year" tenure group to 54.2% in the "> 15 year" tenure group. Chi-square analysis indicated that the prevalence of upper extremity discomfort among tenure groups were statistically significantly different (Chi-square = 16.6, $p < 0.01$). A similar trend was found for both male and female respondents. However, statistically significant difference in the prevalence of discomfort among job tenure groups was found only with the female respondents (Chi-square = 14.6, $p < 0.01$). Across all tenure groups, the prevalence of discomfort was always higher among the female groups than among the male group.

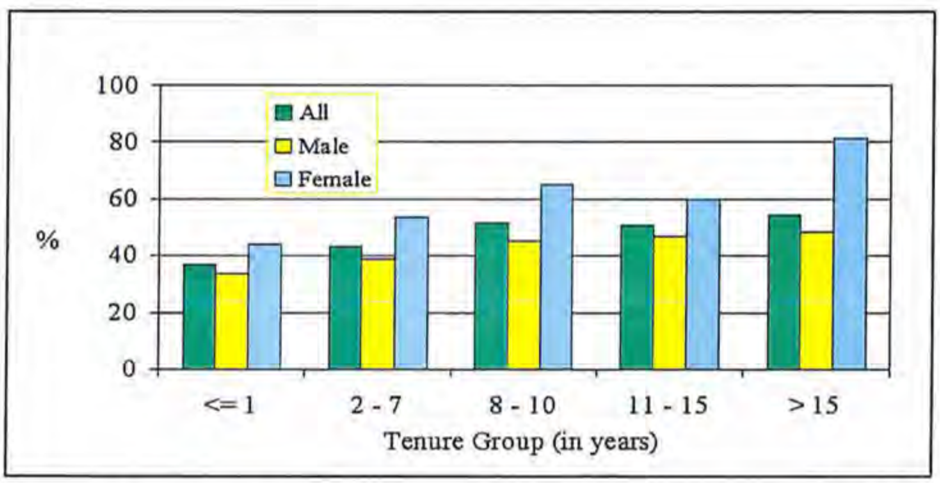

Figure 4. Prevalence of Self-Reported Upper Extremity Discomfort by Tenure

Prevalence of discomfort by the number of hours of computer usage
Figure 5 shows the relationship between the prevalence of discomfort and the number of hours per day spent on the computer. It seemed that as the number of hour of computer usage increased the prevalence of discomfort increased (Chi-square = 92.2, $p < 0.01$). Overall, the prevalence of discomfort increased from 20% for the "less than and equal to 2 hours/day" group to 66.7% for the "greater than 8 hours/day" group. Similar trends were observed in the male and the female respondents.

It is also interesting to note that if one defines "intensive keyboarding" as "spending more than 4 hours/day on the computer," there seemed to be a large increase in the prevalence of discomfort from the "non-intensive keyboarding group" to the "intensive keyboarding group." This was observed for both male and female respondents.

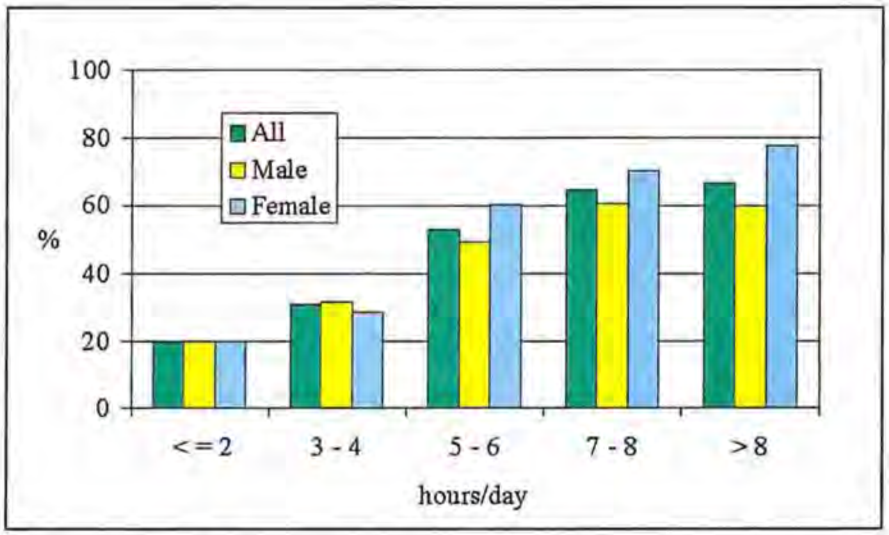

Figure 5. Prevalence of Self-Reported Upper Extremity Discomfort by Computer Usage

Prevalence of discomfort by age group
Figure 6 shows the prevalence of upper extremity discomfort among five age groups. Chi-square analysis showed that age was a significant factor (Chi-square = 16.7 year, $p < 0.01$). From group I (<= 35 years) to group II (36-40 years), there was an increase in the prevalence of discomfort. This was especially obvious for the female respondents. As the age increased from group II (36-40 years) to group III (41-46 years), there was a decrease in the prevalence of musculoskeletal discomfort. The prevalence of upper extremity discomfort started to level off after group III. For male respondents, the age difference in prevalence of discomfort was not statistically significant (Chi-square = 6.1, $p > 0.05$), for female respondent the difference was statistically significant (Chi-square = 26.9, $p < 0.01$). Across all age groups, the prevalence of discomfort among the female respondents was always higher than that among the male respondents.

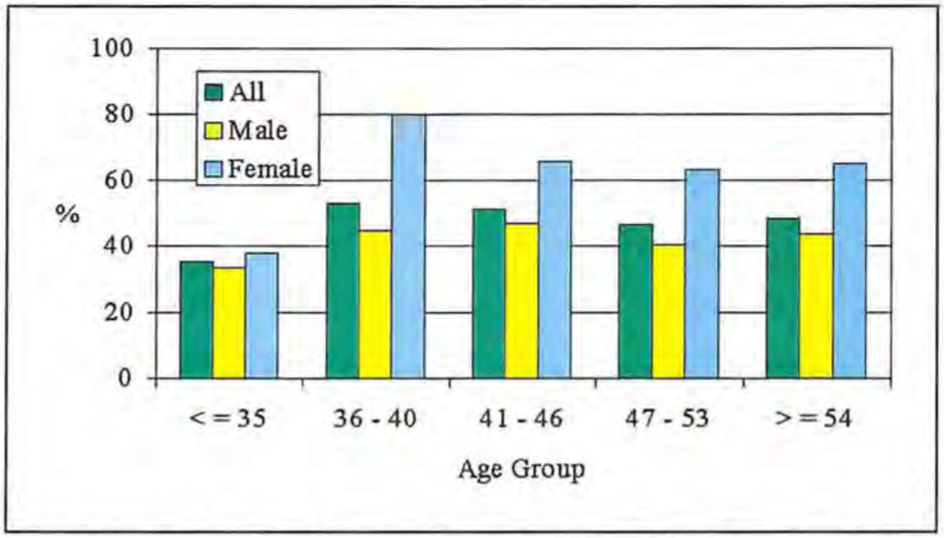

Figure 6. Prevalence of Self-Reported Upper Extremity Discomfort by Age Group

Prevalence of discomfort among respondents wearing bifocal glasses
Figure 7 shows that upper extremities discomfort tends to be slightly more prevalent among respondents with bifocals than those without bifocals. However, this is only true for the female respondents. For the male respondents, the prevalence of upper extremity discomfort was about the same for both groups, with and without bifocals.

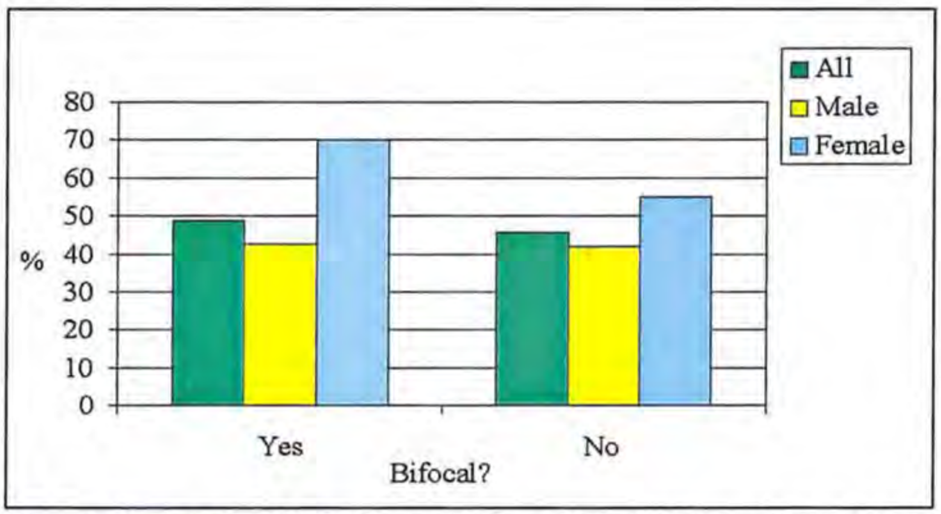

Figure 7. Prevalence of Self-Reported Upper Extremity Discomfort by Bifocal

Prevalence of upper extremity discomfort and job function
Figure 8 gives the prevalence of upper extremity discomfort and job function. Engineers and managers seemed to have slightly lower prevalence, 41% and 43% respectively, than administrative personnel and personnel in other job functions, 56% and 52%. This trend was more obvious among female respondents than among male respondents.

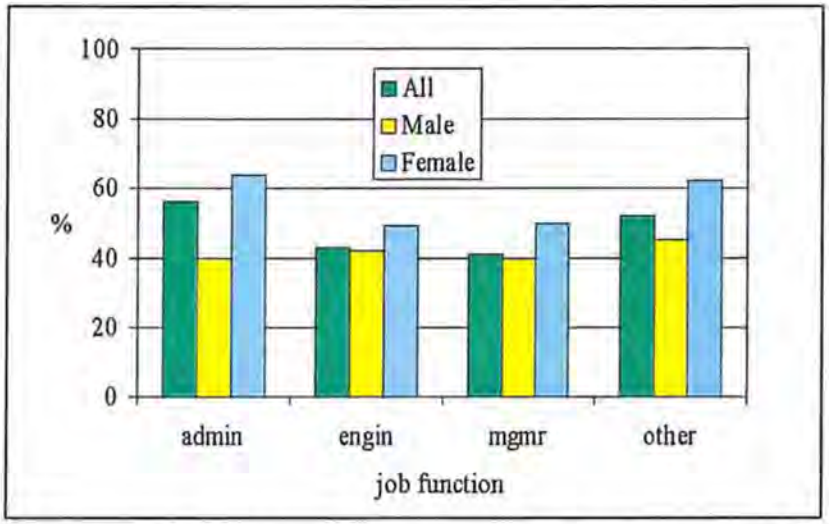

Figure 8. Prevalence of Self-Reported Upper Extremity Discomfort by Job Function

Perceived Work Demand in Keying and Using Mouse

Respondents gave self-perceived work demands in keying and using mouse as "continuously," "intermittently," and "rarely." 70% of the respondents regarded their computer work as requiring them to key or use the mouse "intermittently." 15% of the respondents perceived their computer work as requiring them to use the keyboard and mouse "continuously" and another 15% of the respondents regarded the demand was "rarely." 28.6% of the "rarely" group, 46.5% of the "intermittently" group, and 64.9% of the "continuously" group reported musculoskeletal discomfort of the upper extremity. Chi-square analysis gave a Chi-square of 39.0 ($p < 0.01$) indicating a statistically significant association between the self-perceived work demand in keying and using mouse with the self-reported experience of upper extremity discomfort.

Frequency of taking breaks away from computer work

Respondents were classified into four groups based on the self-reported frequency of taking breaks, i.e., "> 4/hr," "2-3/hr," "1/hr," and "< 1/hr." As shown in Figure 9, 31.4% of the "> 4/hr" group (n=172), 38.5% of the "2-3/hr" group (n=288), 53.5% of the "1/hr" group (n= 254), and 59% of the "< 1/hr" group (n=273), reported musculoskeletal discomfort of the upper extremity. A Chi-square analysis crude analysis yielded a Chi-square value of 45.2 ($p < 0.01$). It appeared that respondents that took fewer breaks were more likely to report upper extremity discomfort than the respondents that took more breaks did.

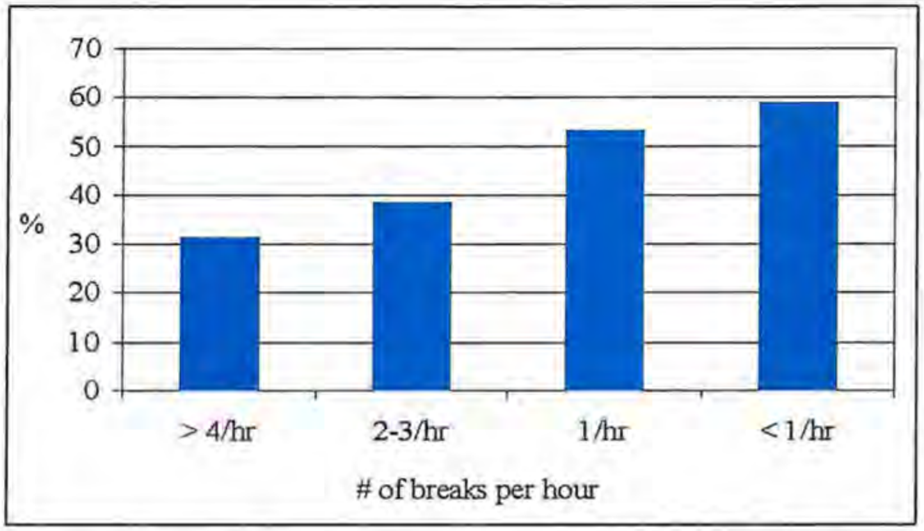

Figure 9. Prevalence of Self-Reported Upper Extremity Discomfort by break pattern

Logistic Regression

Using a logistic regression model, we evaluated the association of the prevalence of self-reported upper extremity discomfort with age, gender, tenure, hours of computer usage, use of bifocal, and job function. Age of the respondent was treated as a continuous variable in the model. Gender, and groups formed based on job tenure, hours of computer usage, job function, frequency of breaks, and perceived computer work demand, were treated as categorical variables. The results indicated that gender was significantly associated with the prevalence of self-reported upper extremity discomfort. Female respondents were more likely to report musculoskeletal discomfort of the upper extremity than male respondent did. The odds ratio was 1.4 ($p < 0.05$) with a 95% confidence interval (95%CI) of 2.06 and 1.03.

Logistic regression analysis also showed that computer usage in hours/day was significantly associated with the prevalence of self-reported upper extremity discomfort. Using Group I (<= 2 hours/day) as the reference group, the odds ratios ranged from 1.88 (95%CI: 1, 3.54) for group II, 4.15 (95%CI: 2.21, 7.8) for group III, 6.22 (3.17, 12.2) for group IV, to 7.63 (95%CI: 2.62, 22.21) for group V, respectively. All were statistically significant at the 0.05 level. Trend test gave a slope of 1.39 and its standard error of 0.36. The 95%CI is (0.68, 2.09), indicating a positive trend in the odds ratio with increasing exposure.

Logistic regression analysis also showed that job tenure was significantly associated with the prevalence of upper extremity musculoskeletal discomfort. In this analysis tenure group I (< = 1 year job tenure) was used as the reference group. The odds ratios for groups III to V were 1.84 (95%CI: 1.21, 2.78), 1.68 (95%CI: 1.07, 2.65) and 2.13 (95%CI: 1.31, 3.44), respectively, all significant at the 0.05 level. There was no significant increase in the prevalence of upper extremity discomfort as the job tenure increased from group I to Group II. Trend test yielded a slope of 0.29 with a 95%CI of 0.14 and 0.45, indicating a positive trend in the odds ratios with increasing job tenure.

Frequency of taking breaks from computer work also was shown by the logistic regression analysis to be a factor significantly associated with the prevalence of upper extremity discomfort. Respondents that took either one break/hours or less than one break/hour were more than twice likely to experience musculoskeletal discomfort of the upper extremity than those respondents that took more than 4 breaks/hour did. The odds ratio for the "less than 1 break/hour" group was 2.2 (95%CI: 1.42, 3.42) and the odds ratio for the "1 break/hour" was 2.1 (95%CI: 1.38, 3.28). Trend test yielded a slope of 0.3 with a standard error of 0.1. The 95%CI of the slope was (0.1, 0.5), indicating a positive trend in the odds ratio with less frequent breaks.

Discussions

This study showed that 47% of the respondents in this particular engineering firm experienced musculoskeletal discomfort of the upper extremity. This result is consistent with the prevalence of musculoskeletal discomfort/disorders of the upper extremity reported in the literature. For example, Arras (1994) found a prevalence of 30.5% of neck/shoulder discomfort among VDT users. Bergqvist et al. (1995a, 1995b) in studies of office workers found that the prevalence of neck/shoulder discomfort was around 60%. In a study of 3,000 workers in editorial, circulation, classified advertising and accounting departments, Bernard et al. (1994) reported a prevalence of neck discomfort of 26%. Among female data entry workers, the prevalence of neck discomfort found by Kukkonen et al. (1983) was 47%. Ryan and Bampton (1988) reported similar prevalence of neck/shoulder discomfort, 44%, in their study of data processing operators.

This study also found that the number of hours of computer usage was significantly associated with the prevalence of self-reported musculoskeletal discomfort of the upper extremity in the engineering firm. As the number of hours of computer usage increased the prevalence of upper extremity increased. This finding is similar to that reported by Rossignol et al. (1987). In their study of 191 workers involved in computer and data processing, the prevalence of neck discomfort increased 39% for "0.5 –3 hours" of VDT use to 61% for "7 or more hours" of VDT use. Similarly, Yu and Yong (1996) found with 151 VDT users in a Hong Kong bank that frequent VDT users were more likely to report neck discomfort than infrequent VDT users.

The study showed that respondents who took fewer breaks were more likely than respondents who took more breaks to report musculoskeletal discomfort of the upper extremity. This suggests that computer workers should take more breaks from computer work to prevent musculoskeletal discomfort, as recommended by other researchers and by many professional ergonomists. (Henning et al., 1989, 1993, 1997) However, as there were still more than 30% of the respondents in the group that took "at least 4 breaks/hour" felt upper extremity discomfort, more frequent breaks seem to be needed.

Because of the exploratory nature of the pilot study, several less than desirable features of the study need to be noted. First, non-specific body joint discomfort was used as the endpoint. Discomfort in the neck, shoulders, elbows, wrists and hands were all grouped together. Back discomfort was not included in the phrasing of the question. Second only self-reported hours of computer usage and self-perceived musculoskeletal discomfort were included in the study. As the experience of musculoskeletal discomfort might have affected the self-reported number of hours of computer usage, a more objective means of quantifying the use of computer need to be designed.

Third, the apparent response rate, 22%, seemed low, based on the number of the employees, 4,576, at the time of the survey. However, the actual response rate could be higher since the ergonomic team only distributed the initial invitation through departmental managers. There is a possibility that a portion of the managers did not pass on the invitation to their employees. Subsequently, the employees of the department would not have the chance to respond. The again points to the importance and need for a planning a survey through Internet, despite of the fact that this study demonstrated the feasibility and efficiency of using Intranet as a means of conducting discomfort survey.

Conclusions

Musculoskeletal discomfort of upper extremity was shown in this study to be common among employees in this particular high tech engineering firm. Four factors associated with the prevalence of self-perceived upper extremity musculoskeletal discomfort are gender, number of hours of computer usage, frequency of taking breaks, and job tenure. The study also demonstrated that the feasibility and efficiency in using Intranet as a means for discomfort survey.

Acknowledgment

The authors would like to thank the members of the ergonomics team of the engineering firm in collecting the data.

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A Software-Based Tool for Exposure Assessment of VDT Work through Internet - Subproject II

Abstract

There is a need for an objective exposure assessment tool to evaluate the association between task demands and musculoskeletal discomfort/disorders commonly experienced by workers that use visual display terminals (VDT). This paper (1) describes the process involved in the development of a software-based tool designed for exposure surveillance of VDT work through Intranet and Internet; and (2) presents the results of laboratory validation and preliminary feedback from a pilot field evaluation. The software-based tool consists three components. The first component intercepts the signals from the keyboard and the mouse. The second component, based on the assumption of a touch typist and the keyboard signals intercepted, increases the number of counts of nine counters designated to fingers of the two hands. Every second the program writes the resultant counts of all the counters into a data log file. The third component of the program uploads the log file to a central network server at the end of the work shift for data collection and further analysis. Laboratory simulations gave satisfactory results in tracking the signals from keyboard and mouse, finger assignment, and file transfer from local computer workstation to central server through Intranet and Internet.

Keywords: Exposure Surveillance, VDT, Computer, Mouse, Keyboard

Introduction

Musculoskeletal discomfort and pain in the shoulders, neck, back, and hand/wrist are common among visual display terminal (VDT) workers.[1-7] Hagberg and Wegman showed that use of VDT for more than 20 hours per week was associated with excessive risk for certain musculoskeletal endpoints.[8] Bergqvist reported that increased keyboard use increased the risk of hand/wrist problems.[9] Foglman and Brogmus, based on the workers' compensation data, found that musculoskeletal disorders associated with computer mouse use appears to be a growing problem and deserves more research.[10]

However, field evaluation of the association between VDT work and musculoskeletal complaints is in general hindered by a lack of objective measurement of exposure. Self-reported VDT work duration tends to be the measure of the physical demands posed by VDT in most studies. Self-reported exposure is prone to bias. And work duration as a surrogate of exposure only gives a partial picture of the physical demands associated with VDT work, as intermittent short break and variation of office activities may reduce the total physical demands of VDT work.[11, 12]

An objective exposure assessment tool is needed to improve the quality of exposure estimate in epidemiological study and to facilitate health surveillance in VDT work. This ideal tool should have at least the following characteristics. First, it should be reasonably accurate in providing an estimate of not only the total duration of VDT work but also the pattern of the intermittent breaks. Second, it should be relatively in expensive and easily installed in many VDT workstations so that exposure could be estimated for as many VDT operators as possible. Third, it should require minimal, if any, operator training and involvement in using the surveillance tool. Fourth, it should not affect the productivity of VDT operators. Fifth, it should be relatively easy for data collection and analysis so that feedback to the VDT operators could be provided relatively quickly. As keyboard and mouse represent two major input devices in PC-based VDT work and as Intranet and Internet are becoming more prevalent in modern office environment, an exposure surveillance tool satisfying the above criteria may be developed.

This paper describes the development of a software-based exposure assessment tool and presents the preliminary results of evaluation in the laboratory. This software-based exposure assessment tool is designed for VDT workstation using Microsoft Windows based system. The tool tracks and categorizes the signals second by second from the keyboard and the mouse. The resultant counts of keystrokes and mouse-clicks are saved in a log file in the local computer then uploaded to a central server for data processing. A unique feature of the software-based tool is that all data collection is conducted through Intranet and Internet.

Methods

Program Development

As many personal computers nowadays operate under Windows based operating systems, the software-based exposure assessment tool was developed for Windows based system. The Windows-based operating system handles keyboard and mouse signals and sends these signals as messages to the software program that is active at the time of data input. This active application program could be a word processing program, a spreadsheet program, or a web browser. This event-handling property of the Windows operating system is the basis for the development of the software-based exposure assessment tool described in the present paper.

The software-based exposure assessment tool consists three components. The first component captures the signals from the keyboard and mouse. The second component increases the count of a counter assigned for a specific finger, assuming that a touch typist enters the keyboard input. The third component uploads individual exposure record from multiple VDT workstations to a central server. Figure 1 outlines the programming logic in a flow chart.

Component I. Tracking Keyboard and Mouse Signals at Individual VDT Workstation

The first component was developed using an Object Link & Embedding (OLE) program in Visual Basic 4. This OLE program intercepts signals from keyboard and mouse; gives the necessary Window messages, including those messages specifically for keyboard and mouse signals; and returns an identification number of the message intercepted. Based on the identification number returned, the keyboard and mouse signals were identified and recorded. In addition to tracking the signals from the keyboard and the mouse, this OLE program also allowed us to track the active window, i.e., the active application software, for which the keyboard or mouse signals were intended. For example, if the VDT user was using a word processing program and entered several keys, not only the keyboard signals will be tracked but also the name of the word processing program and the file name of the document could be tracked.

"Keyboard Input"

A typical keyboard has 101 keys. According to their function and where they located on the keyboard, they could be grouped as alphanumerical keys, function keys, cursor movement keys, and numerical pad. There are 58 keys on the section for alphanumerical keypad, though some of the newer keyboards have additional keys, such as "turbo" and "Windows Start" keys. There are twelve function keys and one 'Escape" key on the top row of the keyboard. Three system keys: "Print Screen", "Scroll Lock" and "Pause", are also located on the top row. Six keys for "insert," "delete," "home," "end," "PageUp," and "PageDown," are located in the middle section of right-hand side of the keyboard. Below them are four cursor keys. Seventeen keys are located on the numerical pad.

These keys can also be differentiated as printable keys such as the "a" and "1", and non-printable keys such as the function keys "Escape" and "F1" and cursor movement keys "PageUp" and "PageDown". The printable keys are identified by comparing them directly with the characters represented by the ASCII code. The non-printable keys are identified using their individual virtual key code provided by the Windows message.

Mouse Input

The OLE program installed within the software-based tool also allows us to track the status of mouse movement, and the up and down states of each of the two buttons (left and right) of the mouse. Single click and double clicks can also be differentiated with the software-based tool.

Component II. Finger Assignment based on a Touch-Typist Assumption

A total of nine counters were created to store the keystroke counts. For a touch typist, eight of the nine counters stores the keystrokes made by the four fingers of the left and the right hands. For example, cumulative counts of keystrokes made on "q, a, z, !, Q, A, Z," are stored in one counter created for the left little finger, while that for "2, @, w, W, s, S, x, X" are kept in another counter designated for the left ring finger. The cumulative count of keystrokes made on the "Space" key is kept in the ninth counter designated as "thumbs," since the space-bar on the keyboard can be triggered by either the right or the left thumb. The "Shift", "Ctrl", and "Alt" keys are three sets of keys that can be identified but cannot be differentiated into left or right since they share the same function but located at opposite sides.

Component III. Multiple VDTs Exposure Assessment – File Transfer to a Central Server

This component of this software-based tool was developed using a File Transfer Program (FTP). This component facilitates collecting data from multiple VDT workstations. This component initiates a windows-based program at the end of the data gathering session at individual VDT and calls a file transfer program included in operating systems such as the Windows 95™ or Windows NT™, which then uploads the resultant exposure file to a central server for analysis.

The process of transferring the log file is automatically completed through a script file generated by the software-based exposure assessment tool. The script file includes date and time of exposure data collection, file name, user's login name, and a password, if required by the server's security.

Laboratory Validation

Laboratory validation of the software-based tool was done at the UCLA Occupational Safety/Ergonomics Laboratory. The software-based exposure assessment tool was installed in computers equipped with CPUs made by Intel, Cyrix, and AMD. All computers had at least 16 MB and with connection to UCLA Intranet. Input device used includes a 104-key AT keyboard and a Microsoft mouse or an MS compatible serial mouse. Operating systems tested include Windows95, Windows98, and WindowsNT. The software-based tool was tested with a word-processing software package and a spreadsheet software package.

Counting the Keystrokes - All Keys without Finger Assignment

A virtual keyboard template as shown in Figure 2 was developed for testing the software-based tool. The virtual template has counters arranged in four sections. Sections, I through III, are for keys on a typical keyboard. Each counter of the virtual keyboard template increased by one each time its corresponding key was pressed. We tested each key on a typical AT keyboard by pressing them one by one to verify the increment of each counter. The virtual keyboard template was developed using Visual Basic 4.

Printable Keys without Finger Assignment – Tests with Application Software

During the later phase of software development, a similar, but simplified, test was conducted using a word processing software package and a web browser. This test was done without the finger assignment. A simple sentence, "The quick brown fox jumps over the lazy dog," with all the 26 printable characters included was entered 15 times on a computer equipped with a AMD K6-2 350 MHz CPU and a Windows98 operating system.

Test with Rollover and Chord Techniques without Finger Assignment

Rollover, i.e., pressing the second key while the first key was still down, was tested. Two keys were entered without correction as fast as possible into a text document with a word processing package.

Chord technique, i.e., entering multiple keys simultaneously, in data entry was also tested. Specifically, the software-based tool was tested with 2-key and 3-key chord technique.

A stopwatch was used to time the duration of data entry in the two tests. Number of characters in the document were manually counted and compared with the counts tracked by the software-based tool without finger assignment.

Printable Keys with Finger Assignment

Once a signal from the keyboard is identified, the assignment is a simple process of looking up the specific key in a table and increasing by one the specific counter designated for the finger. A look-up table based on the assumption of a touch-typist is shown in Table I. For printable keys, the software-based tool was tested in a word processing software by tracking the keys with finger assignment. Three lines of printable characters were entered during three trials. The first line included the upper cases and lower cases of 26 alphabetic characters, space keys, and a period. The second line included 9 numbers, and special keys such as "! @ # $ % ^ & * ("and a period. The third line included the rest of special keys, i.e., "'- = [ ] \ ; ' , . / ~ _ + { } | : < > ?" and one period. Cumulative counts of the finger counters provided by the software-based tool was then compared to the predetermined number of finger counts assuming the text was entered without error. These tests were conducted on three computers with three different Central Processor Units (CPUs) such as Pentium 100 MHz and Pentium 133 MHz. Each test paragraph was entered 15 times on each computer.

Tracking the Mouse

The virtual keyboard template of Figure 2 also shows a section for the mouse signals (Section IV). There are 7 counters, five of which are for the single and double clicks of the left and right buttons and the mouse movement. These five signals are tracked with the current version of the software-based tool. The other two counters designated for single and double clicks of middle button of the mouse are for future expansion of the software-based tool.

Single click and double clicks were tested by clicking the buttons of the mouse and by observing the increment of the corresponding counter. The mouse movement was tested with the virtual keyboard template, a word processing software package and a spreadsheet software package.

Mouse Movement

Test of the software-based tool in tracking mouse movement was conducted with virtual template, word-processing software, and spreadsheet software. Two serial mice, one Microsoft and one Microsoft compatible, were tested with a computer equipped with an AMD K6-350 MHz CPU and Windows98 operating system.

Four tests were conducted with each mouse by moving the mouse in four predetermined directions. The experimental set-up, as shown in Figure 3, consists a mouse pointer and a computer monitor on which a rectangle (30 cm x 16 cm) with eight markers was placed. The markers on the screen were numbered clockwise as 1 to 8. The distance between #1 marker and #3 marker was 30 cm measured on the screen. The distance between #1 and #7 markers was 16 cm. Marker #2 was place at the midpoint between #1 and #3 while #4 marker was placed between #3 and #5 markers.

During the first test, the mouse was moved so that the cursor moved twice from #1 marker to and from the #5 marker. In the second test, cursor was moved from #8 marker to and from #4 markers twice. Similarly, the third test was conducted so that the cursor moved twice from #7 to and from #3 twice. In the final test, the mouse was moved so that the cursor moved back and forth from #2 marker to #6 marker. Count increment of the "mouse move" counter was recorded during each test. Mouse movement during each trial was videotaped with a camcorder (Panasonic, OmniMovie) placed perpendicularly to the tabletop. Permanent timecode was also placed on each frame of the videotape using a timecode generator (Horita II, TRG-5). A marker was placed on the mouse to track the position of the mouse.

Validation of the File Transfer Program

File transfer from the local computer to the server is initiated automatically when the software-based software tool is terminated. Files created during these trials were programmed to upload to an FTP server. Two validation tests were conducted. One was conducted by uploading the data files created by the software-based tool from two offices to a server at the micro-computing laboratory managed by the UCLA School of Public Health. The second test was conducted by uploading data files from three computers in the occupational ergonomics laboratory to another computer running an FTP server.

Preliminary Field Test

The software-based exposure assessment tool was pilot tested at an engineering firm by its ergonomics team and information technology group. This engineering firm uses WindowsNT servers and workstations. A computer equipped with an AMD-K6 166 MHz CPU, 64-MB memory and Windows98 operating system was installed on-site as the FTP server. Test runs were conducted to validate the functionality of the software-based tool.

Statistical Analysis

Correlation and regression analysis was done using a personal computer with Statistical Package for Social Science (SPSS).[13]

Results

Printable and Non-Printable Keys

Errors in counting due to programming errors were corrected during the initial phase of the software development process. Each key on the keyboard was tracked without error in the final test.

Test of Finger Assignment

Having adjusted for few errors in data entry during the test, the software-based tool assigned each key of the test phrases correctly.

Test with Rollover and Chord Techniques

In rollover tests, 432 keystrokes and 437 keystrokes were made in 1.09 second and 59 second, respectively, in two tests. On the average, it took about 135 to 160 millisecond to make one single key during the first and second trials, respectively. No difference was found between the count of characters entered in the document and the number of counts tracked by the software-based tool.

In 2-key chord tests, the average duration to complete one set of keys entry varied from 67 millisecond to 120 millisecond. There was no difference between the counts tracked by the software-based tool and that registered in the word document.

In 3-key chord tests, the software-based tool gave zero count and the word processing software registered no character.

Mouse Single Click and Double Clicks

Results of mouse click tests showed no difference between the count increments tracked by the software-based tool and the number of single and double clicks entered. The software-based tool tracked mouse clicks of the left and right buttons without error.

Mouse Movement

Mouse-move counter increased as the mouse was moved. There was high correlation between the mouse-move count increments and the amount of time during which the mouse moved; despite of the fact that two types of mouse and three software were tested. The R-squared values ranged from 0.96 to 0.98. The slope of the regression line relating count increment and the amount of time that the mouse was moved ranged from 0.038 to 0.042 with a stand error of 0.001.

Format of the Output File

Table II shows a sample of the data log file generated by one version of the software-based tool. The first line gives the date and time at which the software-based tool was initiated. The second line gives the names of the eighteen counters tracked by the specific version of the software-based tool. Starting from the third line gives the second-by-second cumulative counts of the keystrokes and mouse activities. There are twenty columns in each line. The first column gives the time in cumulative second for which the data were collected. The second column gives the total number of keystrokes made till the end of the current second. Starting from the third column are cumulative counts tracked for four fingers of the left hand, thumbs, and four fingers of the right hand. Following the counts for fingers is a counter giving the counts of total keystrokes made on the twelve Function Keys. The next two columns give the number of keystrokes made on the cursor movement keys (including insert, delete, PageUp, PageDown, left, right, etc.) and the keys of the numerical pad. The next three columns give the number of counts tracked for mouse clicks (single and double) of the left button and mouse movement. The last column of the file gives the software and the file name when the keyboard and the mouse were tracked.

In this sample, a total of 9,191 keystrokes were entered in 86 minutes. Fifty-two percent of the keystrokes were done by the left hand and forty-eight percent of the keystrokes were done by the right hand, as the person who entered this set of data was a touch typist. Function keys were not used during the 86-minute interval. However, miscellaneous keys were used 552 times and number keys from the numerical pad were entered 29 times. The left button of the mouse was single clicked 161 times and was double-clicked 15 times. Mouse was moved for slightly more than four minutes. The active application software used during this 86-minute interval was Microsoft Word. Figure 4 gives three lines representing the cumulative counts of the keystrokes made by all fingers and by the left and right hands separately during the 86-minute interval. Figure 5 shows the cumulative counts of the mouse usage during the same 86-minute session.

File transfer to server in laboratory and in field

Data files created by the software-based tool were successfully uploaded to the designated servers in laboratory tests at UCLA and in preliminary tests in an engineering firm.

Discussion

In this study we have not only developed a software-based tool for assessing objectively the duration and usage of data input devices involved in the VDT work, but also characterized its functionality in laboratory tests. This software-based tool tracked signals from the keyboard and the mouse accurately and assigned finger usage correctly based on the assumption of a touch typist, except for the three-chord technique.

The software-based tool is inexpensive, since it is software-based and does not require the use of any additional hardware not already installed in the personal computer workstation.

No special training is required to install and use the software-based tool. Installation of the software-based tool is similar to installing any other software. Once installed and initiated, the software-based tool sits quietly in the Windows background collecting data.

Impact on computer productivity seems to be minimal. Our laboratory tests showed that the software-based tool has no apparent negative impact on productivity if the personal computer system is equipped with a 166 MHz or faster CPU, 32 or more MB of RAM and a Windows95 operating system or later. The computer should have at least 8 megabyte of hard disk space in addition to what is needed for Windows operating system, since the resultant data log file for an 8-hour work shift will be about 8 megabyte. As we have only tested the software-based tool with a word-processing and spreadsheet software, further field tests with other application software are needed.

Data collection is easy, as the keystrokes and mouse clicks are stored in an ASCII file ready to upload. For workplace where there is no network, one only needs to compress the file to a diskette. For workplace with network, the data log file from each personal computer workstation is transferred to an FTP server automatically. In both cases, the ASCII file is ready for conversion for data analysis with other software such as a SPSS, SAS, or a spreadsheet program.

Preliminary field tests of installation, usage, and FTP confirmed the results found in our laboratory. The ergonomics team found the software user-friendly and not posing excessive hardware requirement and computer resources. However, the ergonomics team did provide two valuable suggestions for improvement. First, for security reason, the software-based tool is not permitted to track neither the name of the active application software nor the name of the file that a VDT user is working on. Second, assumption of touch-typist is not realistic. More than 30% of the VDT users in the company are not touch typist. The software-based tool has subsequently been modified to accommodate the need of this company.

It should also be noted that the software-based exposure assessment tool applies only to Microsoft Windows-based work environment. Though many VDT operators nowadays work under Microsoft Windows operating system, there are still many VDT operators work with Unix or Macintosh based systems. Similar software-based tool should be developed for these non-Windows VDT users.

Though the software-based tool satisfies our criteria for providing an objective estimate of physical demand of VDT work, the tool could be further improved in several ways. First, the software-based tool does not register signals entered with a 3-key chord technique. This means that usage of 3-key macro in application software will not be tracked. Though we believe keystrokes missed by the software through this mechanism would be low in reality, work is currently underway to find ways to track 3-key chord. Second, the software-based tool in its current form does not differentiate between left and right for "Ctrl", "Shift" and "Alt" keys, since Windows95 operating system does not provide separate left or right messages for these keys.

However, more recent operating systems such as Windows98 and WindowsNT do provide separate left and right messages for these three keys. If there is a need to differentiate these keys in the future, the software-based tool could be refined to provide such a measure.

Only serial mouse has been tested so far with the software-based tool. There are other types of mice, such as Universal Serial Bus (USB) based mouse, and other types of input device, such as digitizing tablet, on the market. The response of these input devices should be tested.

Conclusion

A software-based tool for objective exposure assessment in VDT work was developed and characterized. This tool tracks and categorizes the signals second by second from the keyboard and the mouse. The software can help computer users acknowledge how many keystrokes from each finger during the certain period of keystroke activities and the amount of mouse click status. It also monitors computer usage patterns over time and trend to collect the repetitive keyboard and mouse usage.

The quantification of keyboard and mouse-related activities will provide an objective exposure estimate needed for the establishment of an exposure-response relationship between musculoskeletal discomfort and disorders and VDT work. The software-based tool will form a foundation for future epidemiologic studies of VDT-related musculoskeletal discomfort/disorders.

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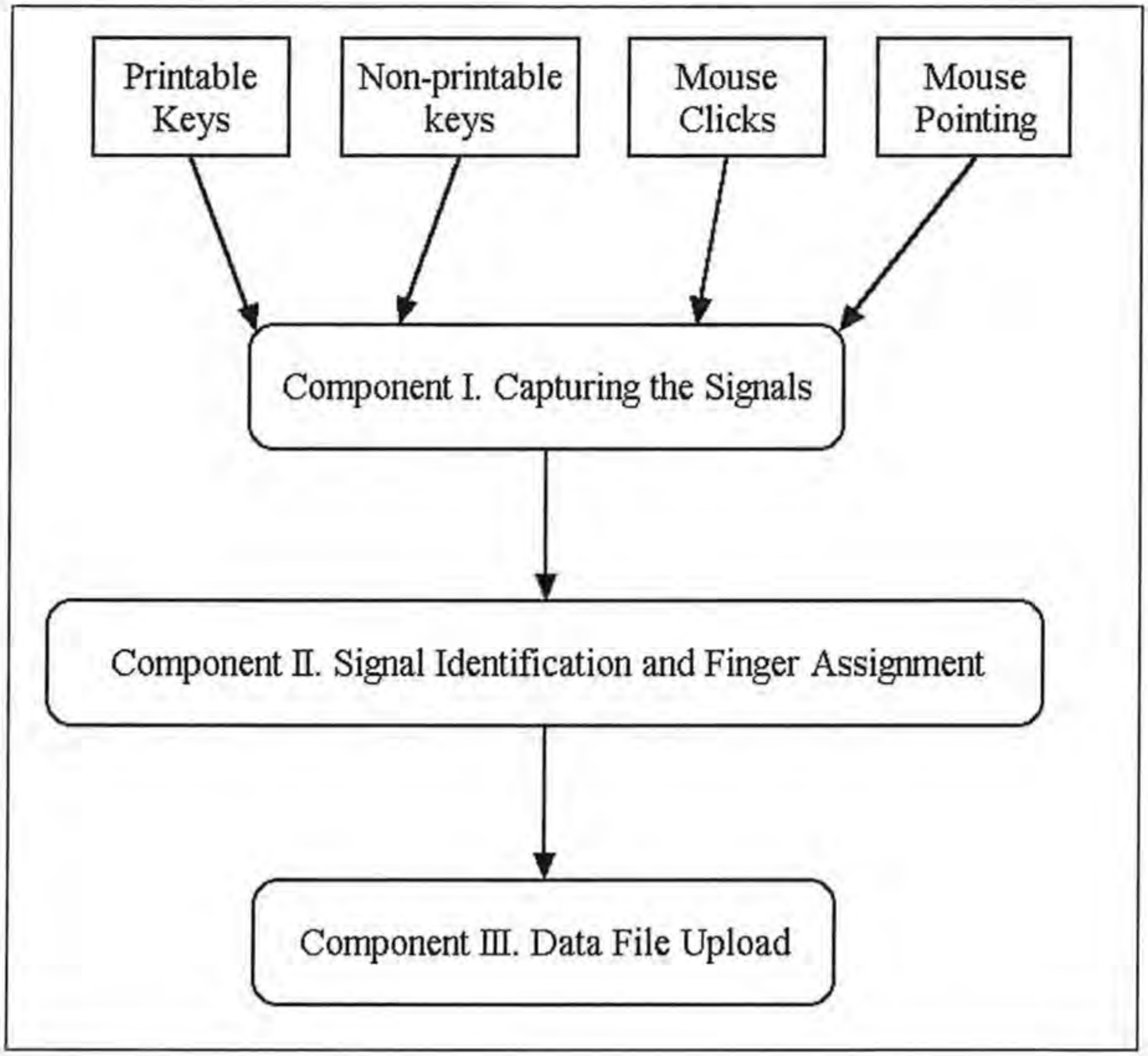
Figure 1. Program Components



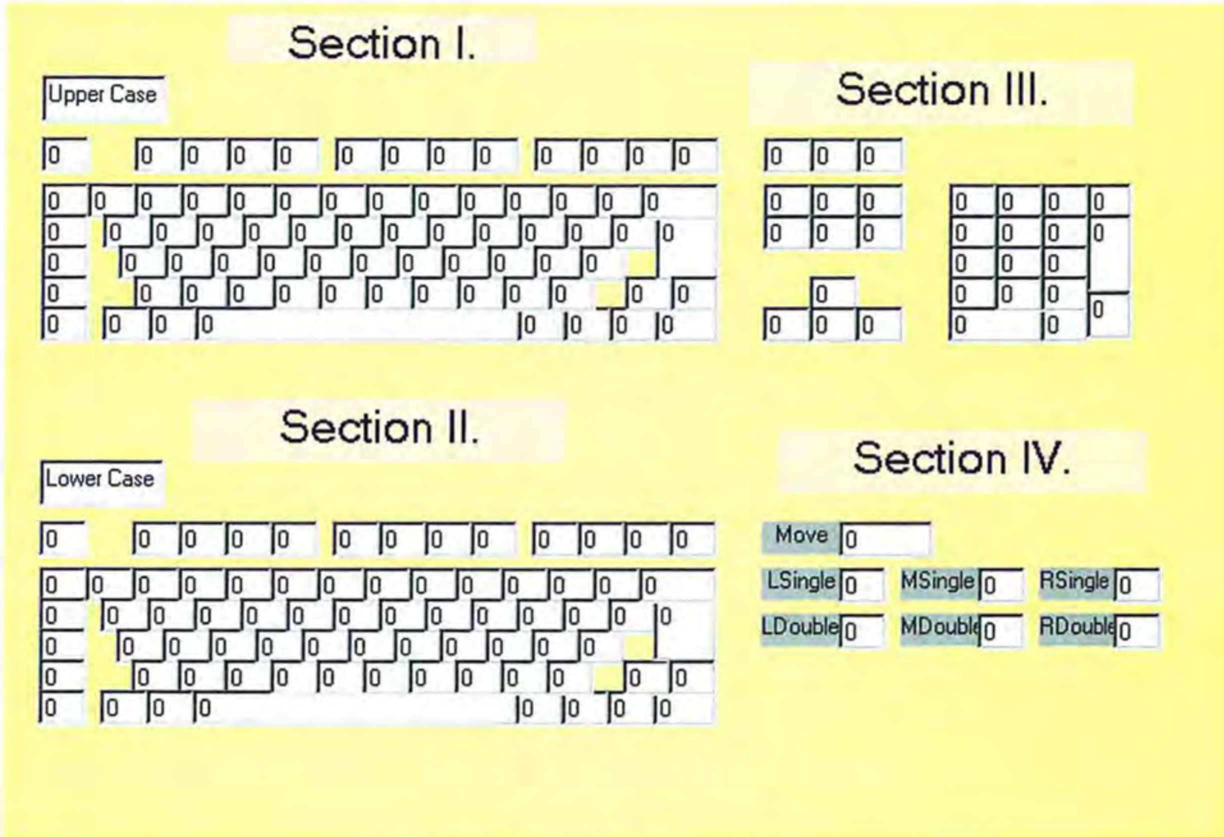


Figure 2. Virtual Keyboard

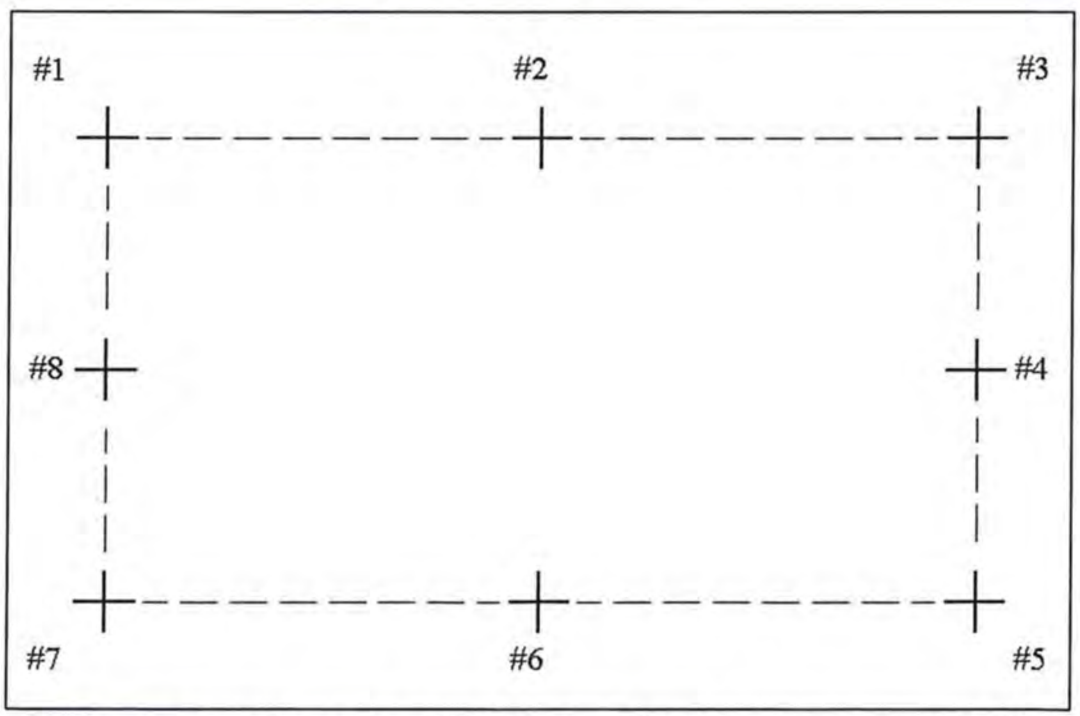


Figure 3. Experimental setup to validate the tracking of mouse-movement with the software developed in the present study.

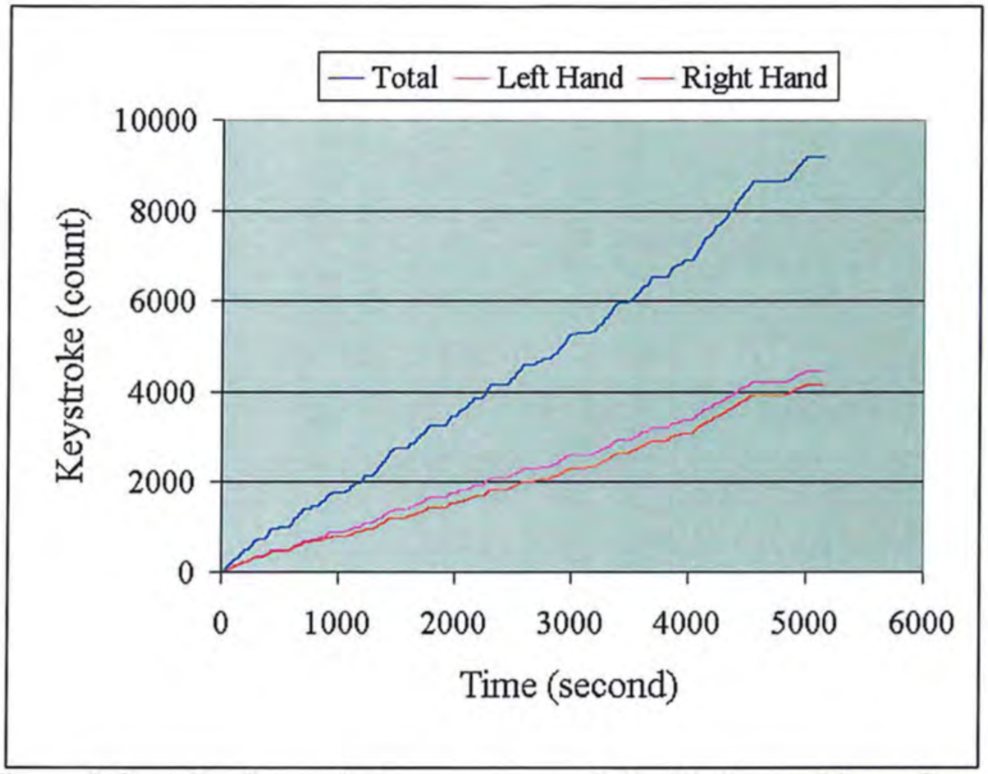


Figure 4. Sample of cumulative counts recorded with the tracking software.

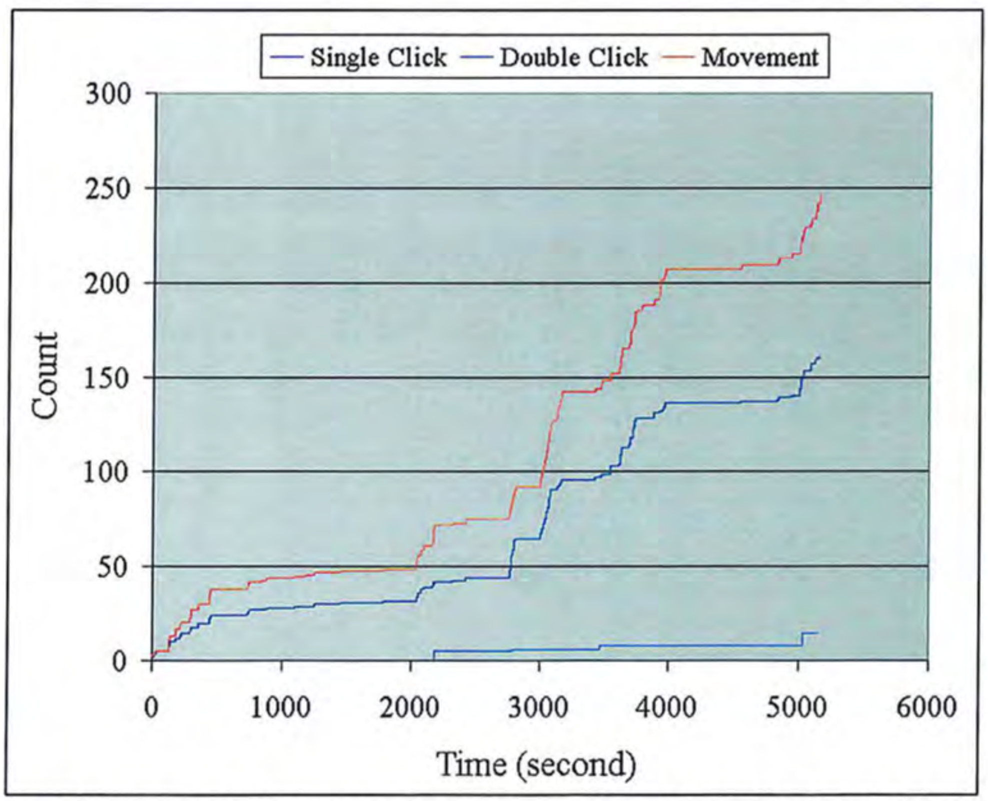


Figure 5. Sample of cumulative count of mouse usage recorded with the tracking software.

Table I. Touch-typist look-up table for finger assignment

Finger	Keys				
Left Little	Esc	~	!	Tab	Q
	Caps	A	Shift(Left)	Z	Ctrl(Left)
	Alt(Left)				
Left Ring	F1	F2	@	W	S
	X				
Left Middle	F3	#	$	E	D
	C				
Left Index	F4	%	^	R	T
	F	G	V	B	
Thumb	Space	Num 0			
Right Index	F5	F6	&	Y	U
	H	J	N	M	Print Scrn
	Insert	Delete	Arrow Left	Num Lock	Num 7
	Num 4	Num 1			
Right Middle	F7	*	(	I	K
	<	Scroll Lock	Home	End	Arrow Up
	Arrow Down	Num /	Num 8	Num 5	Num 2
Right Ring	F8	)	O	L	>
	Pause	Page Up	Page Down	Arrow Right	Num *
	Num -	Num 9	Num 6	Num 3	Num .
	Alt (Right)				
Right Little	F9	F10	F11	F12	_
	+	|	Back Space	P	{
	}	Enter	:	“	?
	Shift(Right)	Num +	Num Enter	Ctrl (Right)	

Table II. Sample data log file

6/27/98	13:38:07													
T(s)	TK	LL	LR	LM	LI	TH	RI	RM	RR	RL	Func.	Misc.	Num.	LMSC
1	0	0	0	0	0	0	0	0	0	0	0	0	0	2
:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
5158	9191	889	449	1181	1318	1233	1079	606	888	967	0	552	29	161

*T(s): cumulative time in second
TK: cumulative count of keystrokes
LL: cumulative count of keystrokes – Left little finger
LR: cumulative count of keystrokes – Left ring finger
LM: cumulative count of keystrokes – Left middle finger
LI: cumulative count of keystrokes – Left index finger
TH: cumulative count of keystrokes – Thumbs (space bar)
RI: cumulative count of keystrokes – Right index finger
RM: cumulative count of keystrokes – Right middle finger
RR: cumulative count of keystrokes – Right ring finger
RL: cumulative count of keystrokes – Right little finger
Func.: cumulative count of keystrokes – Function keys
Misc.: cumulative count of keystrokes – Miscellaneous keys (PageUp, PageDown, etc.)
Num.: cumulative count of keystrokes – Numerical Pad
LMSC: cumulative count of mouse clicks – single click of left mouse button
LMDC: cumulative count of mouse clicks – double click of left mouse button
MMC: mouse-move duration in second

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Hazards in Glovebox Operations in a Defense/Nuclear Facility - Through Ergonomic Task Analysis - Subproject III

Abstract

Two ergonomic task analyses were conducted of two glovebox operations in a Defense/Nuclear Facility. The primary goal of the ergonomic task analyses was to identify factors that might have contributed to the development of musculoskeletal discomfort/disorders among glovebox workers and to the relatively high incidence of glovebox glove failure. The ergonomic job analysis consisted of task analysis through on-site observations and of interviews with experienced glovebox workers.

The first ergonomic task analysis was conducted of an operation that casts metal inside a glovebox. The specific aim of this analysis was to identify opportunities for continuous improvement in terms of reducing musculoskeletal load. The ergonomic task analysis, consisting of task analysis, postural analysis, and static strength modeling, was applied to two on-site simulations and to actual casting operation recorded on videotape.

The results of the postural analysis indicate that the work environment and the tasks involved in casting operation do occasionally place the operators in awkward posture. As a result, the working conditions should be modified sometime soon. The results of static strength modeling show that several tasks involving lifting heavy molds are not designed for the majority of the general population. These tasks could be modified by rearranging the internal layout of the glovebox and by installing auxiliary material handling devices in the glovebox.

The second ergonomic task analysis was conducted of an operation that refines metal in specific forms. This particular glovebox operation has experienced high frequency of abnormal glove breaches. The specific aim of the analysis was to identify improvements that could reduce the incidence of glovebox glove failures. Document reviews, individual interviews, small group meetings, and on-site observations were conducted during the investigation. The results indicate that there are many micro and macro ergonomic improvements that could be made to increase the reliability of the glovebox gloves and the comfort of the workers.

Background

Glovebox, as an enclosure with gloves with confinement to or from the atmosphere using low differential pressure, is utilized as the first and primary defense to protect the safety and health of workers in many operations handling highly hazardous materials. Guidelines to ensure the integrity, in terms of design and fabrication, of the glovebox has been available for many years (AGS, 1998). However, the design of operations to be performed in the glovebox has received relatively little attention, especially in terms of the ergonomics. As a result, misuse and false reliance may give rise to other types of hazards, such as musculoskeletal discomfort/disorders, or may reduce the degree of protection offered by a "properly designed and fabricated" glovebox.

Anecdotal data in a facility that utilizes glovebox extensively have shown that musculoskeletal discomfort/disorders are common among glovebox workers. In addition, the facility has experienced frequent glove changes due to both normal glove wear and abnormal glove breaches. This paper reports the results of two ergonomic evaluations of glovebox operations in this particular facility. The goals of these ergonomic evaluations were to identify factors that may have contributed to musculoskeletal discomfort/disorders among glovebox workers and to the relatively high incidence of glovebox glove failure.

Two ergonomic task analyses were conducted of two glovebox operations in a Defense/Nuclear Facility. The goals of the ergonomic task analyses were to identify factors that may have contributed to musculoskeletal discomfort/disorders among glovebox workers and to the relatively high incidence of glovebox glove failure. The ergonomics job analysis consisted of task analysis through on-site observation and interview.

The first ergonomic task analysis was conducted of an operation (Operation I) that casts metal inside a glovebox. The objective of the analysis was to identify opportunities for improvement in terms of reducing musculoskeletal load associated with glove box operation. The concern for musculoskeletal discomfort and disorders arose from the results of an in-house survey that showed that 57% of the glovebox operators experienced back disorders and more than 24% of the operators experienced neck and shoulder discomfort. As this evaluation was primarily concerned with physical demands aspect of human-machine interface, it is considered as a micro-ergonomics analysis (Hendrick, 1991).

The second ergonomic task analysis was conducted of an operation (Operation II) that has experienced high frequency of abnormal glove breaches. The objective of the analysis was to identify opportunities for improvement in terms of reducing an increasing incidence of failure of Hypalon gloves utilized in glovebox operations. As the foci of this ergonomic evaluation were not only on interface between human and hardware but also on formal rules and procedures, and information and decision support systems, the second ergonomic evaluation considered both micro and macro-ergonomic issues, as described by Hendrick (1991, 1995).

Lead-loaded Hypalon gloves (North Safety Product), 30 mil in thickness, were used as a primary protective device to protect the glovebox operators from radiation in this Defense / Nuclear facility. At the time of the analysis, there was more than thirty glovebox operations in this facility and more than 4000 pairs of glovebox gloves are in use each day at this facility.

Glove changes due to abnormal breach poses risk of radiation exposure. Premature change of gloves increases not only the amount of radioactive waste but also the risk of radiation exposure. The Defense / Nuclear facility has developed a computer database to schedule glovebox glove changes. The schedule of glove changes based on a rating of the tasks performed in a specific glovebox, the frequency of usage, and the application of a survival analysis.

In a period of approximately two years, more than 1,400 pairs of gloves have been replaced and 5.64% of the replacement was caused by glove failure. During the same period, operation II had 90 pairs of glove replaced and 22.2% of the replacement was due to glove failure. Abnormal glove failure is defined at this facility as failure due to puncture, tear, cut, chemical, and heat. Overall, glove changes due to abnormal wear accounted for only 6.2%.

Methods

Operation I.

The ergonomic job analysis of Operation I was completed in three steps. First, the metal casting operation recorded on videotape was broken down into distinct tasks. A time code was added to the videotape using a timecode generator (Horita, CA). The duration of each task was estimated using the timecode between each distinct task. The duration estimate was verified by experienced casting operators to ensure the task being analyzed was representative of the task typically performed in the operation. The weight and dimension of casting apparatus such as molds and crucible were measured on site.

The second step consists of collecting information on the posture typically adopted by glovebox operators while performing the casting operation. This step was conducted in two on-site simulations. Each simulation included all the tasks in the casting operation except for the melting process since the latter involves only visual monitoring by the operator. One operator with seven years of experience simulated the tasks for a period of 17 minutes and the other operator in training simulated the tasks for 14 minutes.

The Ovako Working Posture Analysis System (OWAS) (Karhu, et al., 1977) protocol was used to classify operators' postures at the neck, arms, trunk, and legs every minute. With the OWAS analysis, one could classify the specific operation into one of the four possible "Action" categories, i.e., none (No Action Required), soon (Remedial Action Soon), very soon (Remedial Action Required Very Soon), and immediately (Remedial Action Required Immediately). The classification of the "Action" category is based on the percentage of duration that an operator spends in a particular posture category.

The third step consists of estimating the percentage of population with sufficient strength in three lifting tasks typically performed in the glovebox casting operation. The estimation was based on computer modeling using the 3D Static Strength Prediction Program (University of Michigan, 1994). Weight and dimensions of objects being handled and the operator's posture were inputs of each computer simulation. Three tasks were simulated. Task I involved the lifting of an empty mold, 11 kg, with one extended arm from the right side of the operator. This scenario represents transferring an empty mold from the compartment between two glove boxes. In task II, a mold with the metal rod inside, a total weight of 17 kg, was lifted with the left arm from the left side of the glove box. The scenario simulates a task retrieving a full mold from the furnace area in the glovebox. Task III involved the lifting of a full mold with both hands in front of the operator's chest. This scenario represents a task in positioning the mold for disassembly.

Operation II.

The methods used in the analysis of the operations include document review, on-site observation, individual interviews, and small group meetings. The focus of this portion of the study was on macroergonomic issues that might be improved to reduce the frequency of glove breach. Macroergonomic approach was adopted in this project because microergonomic approach can sometimes achieve marginal success without resolving simultaneously macroergonomic issues. The macroergonomic issues addressed in this analysis were characteristics of the workforce, information sharing and transfer, and decision-making.

At the time of the analysis there were four staffs and six technicians in Operation II. There was one female technician. The mean age of the staffs and technician was about 40 years. Job tenure ranged from 2 to 10 years. The operations performed in Operation II included ingot-casting, metal extraction, electrorefining, oxide reduction, and salt extraction.

Results and Discussion

Operation I.

Task Analysis

Casting metal rods, in general, consists of sixteen distinct tasks, and usually takes about 45 minutes to complete. These sixteen tasks, as shown in Figure 1, fall into three categories. The first category includes the preparation of a mold and a crucible, loading metal scraps, and setting up the casting apparatus. This preparatory stage takes about 17 minutes to complete, accounting for 39% of the time for metal rod casting. The second category involves melting metal scrap in the crucible and casting the molten metal into the mold. It takes about 20 minutes, 46% of the 45-minute casting time, to complete the melt-and-cast process. The third category includes tasks associated with dismantling the casting apparatus and retrieving four metal rods from the mold. It takes about 15 minutes, 15% of the casting duration, to dismantle the casting apparatus and to retrieve the rods. Tasks in the first and the third categories require direct manipulation by the operator while tasks during melting and casting need only visual monitoring.

Tools used in metal casting are general maintenance tools, such as a hammer, a flat-head screwdriver, a scraper, a pair of tweezers, and a crescent wrench. Though most tools were of lightweight, several tasks did involve the use of extreme force. For example, cleaning residues from the crucible required the operator hammering or scraping with a pointed rod with high force.

The metal casting operation also required transferring objects of various weights, shapes, and dimensions from one end of the glove box to the other end. An empty mold weighs 11 kg and is in the form of a block with 11.25", 4.75", and 3.25" on each side. The mold weighs up to 17 kg after casting. The crucible used was a 3-kg hollow cylinder and 9" in length and 4" in diameter. It weighs 9 kg when it is filled with metal scrap. Constrained by the glove ports and the shape of the mold, the operator was required to grasp the mold with a pinch grip and an extended arm.

Postural Analysis

The postures adopted by an experienced glove box operator in a simulation were the basis of postural analysis of this report. Since operator's posture was not observed during the melt-and-cast process, neutral posture for twenty minutes, a typical duration of the process was assumed.

The results of posture analysis showed that tasks performed inside the glovebox did induce the operator to adopt awkward postures of the neck, arms, trunk, and legs. The operator's neck was in a bent forward and bent backward posture for 23% and 16% of the 45-minute casting operation. The operator's back was in a bent and twisted position for 8% of the time. The operator stood for 11% of the time with both knees bent. The operator worked for 26% of the time with both arms above the shoulder. These results place the metal casting operation in an

OWAS "Action" category as requiring action sometime in the future. One should note that the OWAS protocol gives as prioritizing tool four action categories, i.e., none, soon (action in the future), very soon, and immediate.

However, one should be cautioned in interpreting this set of data. The postural analysis was based on simulated activities without considering the weight of the metal. The posture involved and the duration of materials handling may be different from that in a real working situation. In addition, assumption of neutral posture during the melt-and-cast operation was made in calculating the percentage of time spent in adopting specific posture. This assumption should be verified through work sampling when operators are actually performing specific casting tasks.

<u>Static Strength Modeling</u>

The results of static strength modeling showed that metal casting operation was not designed optimally to suit the capability of the general male population. In general, one should design a task so that at least 99% of male population and at least 75% of the female population have the strength necessary to do the task. However, based on the results of the computer modeling for task I, only 68% of the male population have a strength sufficient to lift the empty mold, 11 kg, with an extended right arm. Elbow and hip were the other two body joints not satisfying general ergonomic design guideline. For task II, the results show that only 7% of the male population has the shoulder strength and only 67% of the male population has the elbow strength to transfer the full mold with one extended arm. Torso, hip, knee, and ankle are joints not satisfying the design guideline. Task III is more easily performed than tasks I and II in terms of more than 95% of the male population capable of doing the task. However, those joints not satisfying design guideline include shoulder, torso, hip, knee, and ankle.

The computer modeling was done without considering the type of grip and the effect of wearing gloves. Lifting with pinch grip, a very poor coupling between the hands and the object, would require the exertion of additional force to lift the mold. This will result in a lower percentage of the population capable of performing the task. Wearing gloves may have a similar effect.

Specific Micro-Ergonomics Recommendations

Operation I. Micro-Ergonomics

There are many potential modifications that one could consider in metal casting operation to reduce the number of lifting and duration required for material handling. The following recommendations were provided to facility's management and operator as ideas for discussion. Nonetheless, these recommendations do not represent a comprehensive list of options. The feasibility, effectiveness, and acceptability of each option should be carefully evaluated by glovebox operators before full implementation.

1. Lower the bucket on the rope system in trunk lines to the same height as the transfer compartment and support the bucket with casters.

2. Place rollers on the transport compartment. The roller could be activated by a small motor.

3. Add a pallet carousel in the glove box next to the transfer compartment and make the top surface of the pallet carousel at the same level as the rollers to be place in the transfer compartment. The pallet carousel could reduce the amount of lifting required by turning the pallet. A 30-inch diameter will fit in the glove box (36" x 32") and is commercially available.

4. Design handle into the mold to facilitate grasping. Avoid using a pinch grip for holding heavy objects such as a mold. Use handles to reduce the distance for reaching the object.

5. Add a tool stand on a 'lazy Susan' and place it on top of the pallet. A tool stand would help organize the tools used in the glove box and reduce the reach distance for retrieving the tools.

6. Use air or electricity powered tools to clean the crucible. A Dremel tool with grinding bits of proper shape should be evaluated.

7. Change the mechanism for removing the cover of the mold shield. Lifting the cover with retractable air cylinder is the current practice. Currently, the operator has to adopt a posture with an extended neck and with the left arm high above the shoulder. The same air cylinder could be used to retract the cover to the glove box on the left hand side that has plenty of unused space. A threaded rod could also be used.

8. Redesign the glass shield into two sections. The shield is light in weight. However, it is not easy to align the glass shield between the crucible and the induction coils, because of the size of the glass shield and of the air cylinders near the ceiling. A smaller section could be reduced the effort in positioning the glass shield. A second section could first be assembled with cover fitted with sensor and stirrer, and then place on top the first section of glass shield already in the desired position.

9. Install an automated adjustable platform to replace the two platforms and the step stool. Though an automated adjustable platform is expensive, it has three advantages. First, it provides accommodation to operators of different statures. Second, it allows easy access to the glove ports at the upper level. Third, it does not present the same hazards as the platforms and step stool do. Sliding the platform away creates a hazard in bumping into the utility lines underneath the glove box. Standing on the step stool to manipulate an object inside the glove box presents a fall hazard.

Operation II. Micro-Ergonomics Issues

<u>Need to integrate ergonomics in current glovebox task design</u>
Glovebox operations, because of its physical design and its requirement of wearing long-sleeve thick gloves, needs more in-depth, detailed consideration of basic principles of ergonomics to optimize human performance capability. Because of the current design of the glovebox task, glovebox operators have to work in a condition that reduces range of motion and dexterity. As a result, operators have to compensate by exerting more force, adopting more awkward posture, and repeating the same manual movements more frequently to get the "job" done. It is no

wonder that glovebox operators appear to be a highly selective group in terms of body build and physical strength. One worker mentioned that it was necessary to build up especially the upper body strength to do the job. These factors, i.e., repetition, additional force, and awkward posture, may increase not only the risks for the operators to develop musculoskeletal discomfort/disorders and the rate of deterioration of glove and increase the chance of breaching the glove.

It is imperative that the management of this Defense / Nuclear facility design the job and select the equipment and tools that will compensate for limitations posed by the glovebox and gloves. The goal of the ergonomic design is to create a man-machine interface with which all glovebox workers could perform the job with less force, less time, and less contact area between glove and objects. However, the current work conditions prove to be the contrary. The management failed in recognizing the need for better tools.

The tools utilized in both Operations I and II, were the usual household maintenance tools. For example, some of the "tools" in Operation II were just steel rods. To make the condition even worse, some of the tools were used in ways for which the tools were not designed. For example, a worker used the pointed end of a file to either knock or scrap impurity off a funnel, while holding the file in his hand. The glove was not only in contact with the sharp edge of the file, but also was being filed by the rough surface of the file. The former condition was a potential cause for cut and the latter condition could be a cause for abrasion, wear and tear. In addition, there was no handle on the file. The pointed end of the file may be a cause for puncture. Other tools, such as the wire brush and the screwdrivers, all had pointed end.

It is recommended that management and the operators hold regular sessions to evaluate the use of each and every hand tool used inside the glovebox and the tool's potential in breaching the gloves. Ways to modify tools or new designs of special tools could be defined through such a brainstorming session. One has to remember that the operators are the true "Experts" in the operation since they have been working in the condition for many years and understand the difficulty involved in utilizing specific tools to accomplish certain tasks. Without management's support and encouragement, they just learn to adapt without thinking there could be a better way. It is the management's duty to provide such supporting atmosphere. Management is nothing more than motivating people.

The equipment in Operation II was also a source of ergonomic concern. Take electrorefining as an example. The workers were required to tighten and loosen six hex cap screws on the flange head of the furnace. The hex cap screw had a width of 0.5 inch, a height of about one-eighth inch, and a thread length of about three-quarter inch. The worker had to align the flange head and turned the screws one by one with a pinch grip. Turning a screw with bare hand was already a task requiring precise thumb and index finger movement and high dexterity. A thick glove would only make it difficult and require more force and time. In addition, the hex cap screw had six pointed angles and sharp edges. High force and sharp edges could be factors contributing to the breaching of gloves. The final tightening of the screws required the use of either an adjustable crescent wrench or a ratchet box wrench. The ratchet box wrench should function much efficiently than the crescent wrench. One should "consult" the workers in terms of reasons of choosing one or the other. Both wrenches still had some potential to stress the gloves.

Operation II was in the right direction in terms of changing from the hex cap screws to a bolt with a T-shape handle. The T-shape handle should be made bigger so that the force would not be concentrated at the ends of the handles and compress the glove.

The stirring rod of the furnace was also a feature requiring some attention. The rod was positioned using several Teflon spacers and a knurled copper ring. The workers would have to tighten it with hand. The knurled ring had ridges very similar to the texture being tested in another study performed by the authors. Obvious wear on the gloves was observed even after 36 hours of testing.

Retrieving the round bottom well-type crucible from the furnace was another task of concern. The worker relied on the friction between eight fingers and the internal surface of crucible to pull the heavy crucible up and out of the furnace. This was not only an awkward lifting job but also a potential contributing factor to the wear and tear of the gloves.

Use of Work-Study

A detailed work-study should be conducted at Operation II to quantify the frequency, force, surface texture, and contact area when Hypalon gloves were used. This type of the study would provide the data necessary to determine the types of stress that a glove has to endure while in service.

The work-study would also be useful in providing information necessary in developing a realistic specification of glovebox gloves, and a protocol for glove testing. At the time of the analysis, this Defense / Nuclear facility initiated the evaluation of the tensile strength of the Hypalon gloves. This endeavor is a good start but needs to be expanded to include more realistic testing conditions.

For example, it is necessary to determine the maximum force that the Hypalon gloves in its current design could endure without being punctured not only for a new glove but also for gloves that have been in service for different period of time. In addition, whether there will be some defects that could be visually identified by glovebox operators under the normal and abnormal conditions should be ascertained. At the time of the analysis, operators were required to visually inspect the gloves through leaded glass windows while wearing the safety glasses. The leaded glass was slightly yellowish tinted and might have been slightly covered on the inside with dust and the glove being inspected was usually covered with dust. The human factors issue in such case can not be ignored especially when the average age of the workforce is around 40 years.

Other testing conditions should be included so that the mechanisms of breaching a glove could all be considered. At the time of the analysis, in Operation II, puncture, cut, tear, and heat were the four main mechanisms to breach a glove, though the work activities and tools that were involved had not been well documented. The tensile strength test being performed would clearly not be relevant if the breaching of glove was due to primarily thermal stress.

Operation II. – Macro Ergonomics Issues

Systematic Approach to Identify Causes of Glove Breach

At the time of the study, the management team seemed to be preoccupied with the idea that high incidence of abnormal glove breach was due to defective glove from the vendor and the aging, i.e., limited shelf lives, of the Hypalon gloves. The management team documented that a defective batch, e.g., with blister, cracking, and discoloration, was received at the facility. However, this was based on only one batch of gloves. The facility needs to establish a program that requires the warehouse or stockroom to sample and inspect the gloves upon receiving each shipment. An alternate would be having the operators examine the gloves when the gloves are signed off at the stockroom.

The effect of aging on glove's service life was only a hypothesis. There were no data to support such a hypothesis. The Hypalon glove is supposedly designed with a feature that minimizes the effect of oxidation. In terms of storage, the manufacturer (North, Inc.) of the Hypalon gloves, recommended laying them on a flat surface and keeping them away from the sunshine. However, once installed on to the glovebox, the glove would most likely hang from the ring (on an active glovebox) or being tied into a knot on a non-active glovebox. On an active box, manual material handling would certainly put the gloves to more stress, probably in regions where the glove has most contact with the objects being handled. This Defense / Nuclear facility should consider a study that evaluates the effect of factors, such as the age, duration in service, frequency of usage, type of manual operation, and temperature, on the reliability of the gloves. The existing glove exchange program could serve as a starting point to link glove failure with task information and manual material handling while wearing gloves.

There may be other factors that have contributed to both the normal wear and the abnormal breach of the glovebox gloves. At the time of the study, the facility relied on the use of survival analysis to schedule the change of the gloves for "normal wear." Though statistical approach, i.e., using survival analysis, seems to be a good method to prevent glove breach and the resultant radiation exposure, it inevitably assumes that the glovebox task is incapable of being modified. The management should take a systematic, proactive approach in applying ergonomic task analysis to glovebox task and identify ways to redesign glovebox task and tools.

Management Information System – A Better Link among Existing Databases

A chart of existing databases at this facility should be created to identify how each database should be linked and how the information could be used to improve the process and to reduce the glove failure. For example, the radiation incidence report available in the facility was not linked with the glove exchange database.

It seems that data on glove usage were being gathered. However, the data collected have not been optimally used. The results of the analysis seem to indicate that this particular Defense / Nuclear facility was not collecting and wisely utilizing the information needed to plan their activities for the prevention of glove breach. At the time of the study, this particular Defense / Nuclear facility did not have a management information system to provide such information.

Communication between Labor and Management

Better communication includes not only verbal and written communication in terms of sharing information and soliciting suggestions, but also a behavioral communication. It is only when a manager puts on his/her coverall, goes through the same manual procedures, exercising the same precautions, and gets a hands-on feel of the difficulty involved in the operation, will the operators feel the sincere concern of the manager and develop trust in the management.

At the time of the study, there seemed to be some doubt as to the intent of the ergonomic assessment work group. Operation II supervisor felt that some workers might perceive the objective of the current study in reducing the incidence of glove breaching as faultfinding. A review of radiation occurrence reports also leads to the suspicion that current incident investigation practice in this defense/nuclear facility could give the operators the impression of faultfinding.

In addition, automation may be an issue of concerns among workers. It is common among many industries that workers become weary about their job security when automation is one of the options being considered by the management. If operators are not asked to participate in decision-making and if the management's intention is not clearly communicated, all other endeavors to improve the work environment, processes, and tools, may well be considered as preparatory steps toward automation. As a result, workers are less likely to provide assistance and receptive to changes.

Rationalization in System Planning

The management team of the facility could benefit from exercising "Rationalization" in system planning. Rationalization is a concept in industrial engineering and industrial management. The purpose of rationalization is to develop and execute an action plan that will result in a simpler, more reliable, more efficient and easier to maintain process, in this case, the glovebox operation at Operation II. This requires a careful examination and reevaluation of the goal of the process and the means to achieve the specific goal. The following two examples identified in the study demonstrate how rationalization could assist in the system planning in this Defense/Nuclear facility.

The first example relates to a new glovebox, housing a big chisel-like breaker and that was being installed in Operation II. The "Breaker" machine would be used to break a metal ring in half for storage because of the limited size of the vault. However, the metal ring took Operation II operators a lot of time and efforts to produce. One should at least consider either modifying the configuration of the metal ring, under the constraint of criticality, or changing the size of the vault for storage. Planning and executing an efficient process, i.e., less contact time, fewer steps, and less use of gloves, is probably the key to success not only in manufacturing and in the prevention of glove breach.

The second example involves the use of a paint scraper to clean salt residues surrounding a chlorine scrubber and on the tabletop of a glovebox. Due to an overflow of chlorine and untimely housekeeping, salt residue formed inside the glovebox. Certainly, one could reduce the potential of chlorine overflow by installing a flow-limiting valve in line, a primary engineering control. Wiping off the salt solution immediately after spills with a rag is probably much safer than using the paint scraper. Once dried, the salt residues formed and adhered to the tabletop rendering difficult to clean. Operator may have to use a sharp object, in this case a paint scraper, to clean the surfaces. It is quite natural for a worker to hold his left hand in front of the scraping action to keep the loose residue in one place. There is a danger of puncturing the left-hand glove if there would be a slip of the right hand with the scraper. Gripping a sharp object in the right hand forcefully for the scraping action increases the potential for cut, tear, and wear of the glove. Timely housekeeping is a part of production activities most people tend to overlook. However, in terms of glove breach, timely housekeeping in the glovebox operation may have a special meaning, despite the fact that current housekeeping in glovebox is much and much better than 10 years ago.

On-line Process Control

During the data collection process through individual interviews and group discussion, the management emphasized many times that retrieving a metal ingot from a crucible could be very difficult and required frequent manual material handling. However, on-site observation revealed that a smooth operation in retrieving the ingot was achievable. The supervisor and the operators gave a 50%-50% chance of having a bad run versus a smooth run. For a process that is important to national security, a 50%-50% chance should not be acceptable. The management and operators should join force in experimenting with the process parameters to identify the causative factors leading to a bad run. Experimental design, using methods similar to the Taguchi method, should be developed and implemented for continuous improvement of the process.

Conclusion

This study demonstrates the utility of a micro- and a macro-ergonomic task analysis for the identification of hazards in a Defense / Nuclear facility. The results of the study showed that the operators involved in glovebox operations were exposed to ergonomic stressors due to the design of glovebox tasks. The study also showed that there were macro ergonomic issues that need to be addressed in order for micro ergonomic issues to be resolved. The safety and health personnel at the facility need to include ergonomic task analysis in their routine hazard surveillance. The management and the workforce should be educated of the importance of ergonomics in continuous improvement of the production process.

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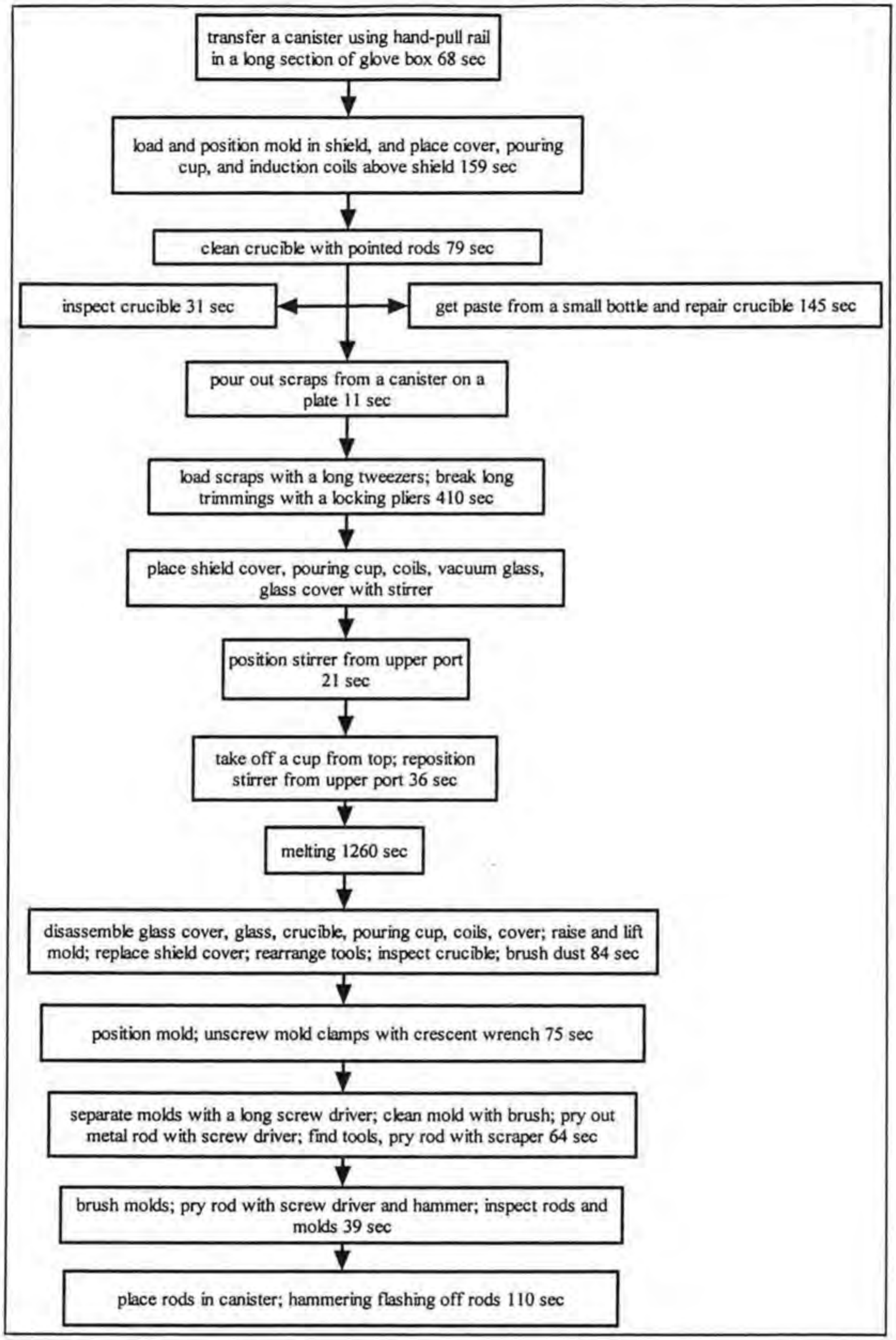
Figure 1. Task flow of casting operation in a glovebox



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Validation of an Experimental Device for the Measurement of Kinetic Friction - Subproject IV

Abstract

An experimental device was developed in this project for the measurement of kinetic coefficient of friction. In addition, the kinetic coefficient of friction (μ_k) of fingertip was measured for six Chinese subjects on textured and non-textured surfaces in this exploratory study. The results indicate that μ_k of the fingertip skin varies with the magnitude of normal force and the surface texture of the test plates. The μ_k decreased as the exerted normal force increased. The highest value of μ_k was 2.05 for males and 2.26 for females with 1 N normal force on a test plate of 100% contact area. When the load increased to 10 N, μ_k decreased to 1.09 for males and 1.11 for females on the same test plate. The μ_k increased as the contact area increased. For males, there was a 39% and 64% increase, respectively in μ_k as the contact area increased from 50% to 75% and 100%. For female, there were, respectively, a 41% and a 77% increase in μ_k as the contact area increased from 50% to 75% and 100%.

Keywords: Kinetic Coefficient Friction; Texture; Chinese.

Introduction

Friction is a common mechanical stressor upon human skin. High friction may produce erosions and blisters to human palmar skin (Knapik et al. 1995). Friction also affects our ability to manipulate and grasp objects with the hand. Friction between the surface of an object and fingers is also needed for an individual to adjust the amount of force applied in manipulating objects (Cadoret and Smith 1996). Low friction objects tend to slip out of the hand resulting in an increase in the potential for injury. Low friction objects therefore require greater grasp forces than objects with high friction. Prolonged, excessive grip forces applied to prevent slippage may cause injuries to tendons and tissues (Putz-Anderson 1988). Armstrong (1985) pointed out the importance of proper friction in the design of hand tools. Frederick and Armstrong (1995) studied the effect of friction and load on pinch force in a simple hand transfer task and suggested that the use of tool handle friction enhancements might reduce required pinch force for objects requiring upwards of 50% or more of maximum pinch strength.

Frictional properties between two surfaces is characterized by the coefficient of friction (μ), a dimensionless ratio of the friction force (F_f) between two bodies to the normal contact force (F_n) pressing the two bodies together (ATSM 1993). There are two types of coefficients, static coefficient of friction (μ_s) and kinetic coefficient of friction (μ_k). Static coefficient of friction, μ_s, is defined as the ratio of frictional force immediately before movement occurs to the normal contact force, while kinetic coefficient, μ_k, is defined as the ratio of frictional force, under conditions of macroscopic relative motion between two bodies, to the normal contact force. Both static and kinetic coefficients of friction are important in the design of hand tools and other manually manipulated objects. The static coefficient of friction of index fingertip has been found to vary with test materials in many studies. For example, when tested with silk, suede, and sandpaper, Johansson et al. (1984) found the static coefficients of index finger and thumb to range from 0.22 to 2.0, while Westling et al. (1984) reported a μ_s, ranging from 0.35 to 1.21.

Smith et al. (1997) reported static coefficients of friction of 1.5 to 1.8 for pinch grip by thumb and index finger against smooth and etched polyamide plastic. However, using the same type of materials, i.e., smooth and etched polyamide plastic, Cadoret et al. (1996) reported static coefficients of friction for barehand ranged from 1.1 to 2.0. On a surface made of aluminum, the static coefficients of friction of finger were found to range from 0.15 to 0.6.

Kinetic coefficients of friction of fingertip have only been reported in a few studies. Tested against rubber surface, the kinetic coefficients of friction of finger skin were found to range from 0.25 to 0.75 (Roberts and Brackley 1990). On textured polycarbonate plates, Bobjer et al. (1993) reported kinetic coefficients of friction varied from 0.56 to 2.22, using a specially designed instrument. Since Bobjer et al. (1993) studied only Caucasian male subjects; there is a need to measure the kinetic coefficients of friction in females and in populations of other ethnicity. It is also of importance to learn whether there is a gender difference in μ_k, since skin compliance and gender seem to be correlated (Woodward 1993). Woodward (1993) defined two measures of skin compliance, a two-point compliance and gap compliance, and found that the hands of males were less compliant than the hands of females. Thus, it would be of interest to learn whether there is a significant gender difference in the kinetic coefficients of friction of fingertip on textured and non-textured surfaces.

In this paper, we report the measurement of kinetic coefficient of friction of the index fingertip against surfaces made of polycarbonate plate. In addition, this study evaluated the effects of gender, magnitude of normal force and surface texture on the kinetic coefficient of friction.

Methods

Instrumentation

To estimate the coefficient of kinetic friction between the skin of fingertip and hand tool surface, a specially designed friction-measuring device was fabricated at the UCLA Occupational Ergonomics Laboratory. This device, as shown in Figure 1, consists of three polycarbonate boards, four friction-less ball bearings, and three strain gauges. The top and bottom boards were positioned horizontally and separated by four ball bearings. The third board was mounted vertically on the bottom board and perpendicular to the top board. This board served as an anchor for the strain gauge.

The top board has a dimension of 24 cm by 14 cm with a thickness of 0.5 cm and a cut-out area of 13.5 cm x 3.5 cm in the center that allows the placement of test plates with specific texture. The top board was supported by the four friction-less ball bearings that sit on the bottom board. The bottom board was clamped onto a table and provided the stability of the testing device. The ball bearings were used to provide free movement of the top board in the horizontal direction.

Two strain gauges were mounted on the edges of the central hollow area of the top plate were used to support the test plate and measure the normal contact force during the test. An additional strain gauge was placed between one side of the top plate and the vertical plate. This strain gauge was used to measure the frictional force. Two types of strain gauges (Omega LCL005 and LCL816) were used in this study. The LCL005 has a maximum capacity of 5-lb force (22.3 N) and the LCL816 has a maximum capacity of 2-lb force (8.9 N). Three LCL005 strain gauges were used for measurement when a normal force of 10 N was exerted. Three LCL816 gauges were used in measurement with 1 and 5 N normal force.

Figure 2 shows a block diagram of the experimental setup for data collection. Two power supplies (Omega model PSS-5A and PST-4130) provided 5 Vdc to the strain gauges. An amplifier (Omega model OCT-01) amplified the analog signal from the strain gauges with a gain of 100. A 16-channel data acquisition board (DAS 1601) and a 486-DX computer were used to collect, process, and display the force measurements. Force measurement was taken at a sampling frequency of 10 Hz during the 3-second sampling duration for each test.

Four test plates made of polycarbonate were fabricated by UCLA Machine Shop. Each plate had a dimension of 13.5 cm x 3.5 cm with a thickness of 0.5 cm and specific surface characteristics. The surface texture of test plates, as adapted from the study by Bobjer et al. (1993), was defined in unit of distance between the ridges and grooves (peaks and valleys). The depth of all grooves was 0.5 mm. As shown in Figure 3, test plate I has a ridge and a groove width of 1.5 and 0.5 mm, respectively. The widths of ridges and grooves of test plate II were both 1mm. Test plate III has a ridge width of 0.5 mm and a groove width of 1.5 mm, i.e., an inverted image of test plate I. Test plate IV has a non-textured surface without ridges and grooves.

Subjects

Three Asian males (age: 31 - 43 years) and three Asian females (age: 25 – 42 years) participated in this study. All these subjects were right handed. Maximum tip pinch strength and palmar pinch strength were measured for each subject using Jamar pinch strength meter.

Protocol

All measurements of kinetic coefficients were taken with dry bare hands. Prior to the start of each session subjects washed their hands with soap and water and used paper towel to clean their hands and maintain dry barehanded condition. The test plates were also wiped and cleaned to maintain a dry and clean condition. The temperature in the laboratory was about 24 °C and the relative humidity was about 44%.

Three normal forces of 1, 5, and 10 N were used for both male and female subjects. Each force-texture combination was presented in random order to the subjects. Several trials were performed before each test, to familiarize the subjects with the procedures and the target force level. Each subject was asked to press the index finger of his/her dominant hand on the test plate and then pull the finger toward himself/herself. Each subject controlled exerted force according to a digital readout displaying the magnitude of the normal force continuously on the screen of a computer monitor. The subjects were asked to keep the normal force within ±10% of the target normal contact force.

Figure 4 shows the data collected during a typical run for the force measurements, normal contact force and frictional force. In this example, 1 N normal force was the target force level. The kinetic coefficient of friction was calculated by taking the ratio of frictional force to normal contact force for each data point. As shown, the exerted normal forces for five data points (from 1.6 to 2.0 seconds) were all within ±10% of the target normal contact force 1 N. Hence, the mean value of kinetic coefficient of friction for this particular example was calculated to be 0.85 by averaging five values of kinetic coefficient of friction from 1.6 to 2.0 seconds.

Monitoring the sliding velocity

During each test, the position of each subject's test finger (index finger) on the test plate was recorded on videotape. The sliding velocity of the finger was later calculated through digitization using a two-dimensional Motion Analysis System (Peak Performance, Inc.). Mean sliding velocity was obtained by averaging five instant velocity measurements taken at the instant of time when the μ_k was determined.

Measurement of contact surface area

The surface contact area was measured by pressing each of the force levels of 1, 5, and 10 N onto a millimeter graph paper placed on top of test plate IV (plain, non-textured surface). The index fingertip was dyed with red ink for a clear impression on the millimeter graph paper. Surface pressure was calculated as ratio of normal force to the surface contact area between the finger pad and the plain non-textured surface.

Statistical Analysis

Data were retained for analysis only if the exerted force was within ±10% of the target normal contact force. If the exerted force was not within the 10% of the desired range, new trials were repeated. For each valid datum, a μ_k was calculated by taking the ratio of frictional force to normal contact force. Mean μ_k was determined by taking the average of five estimates of the μ_k. Descriptive statistics and analysis of variance with repeated measures were performed using the Statistical Package for Social Science (SPSS 1994). The mean and standard deviation of the kinetic coefficient of friction was calculated. In the analysis of variance, the independent variables in this study were gender, texture and normal force level. The dependent variable was the estimates of kinetic coefficient of friction. Analysis of variance with repeated measures was used to evaluate the main effects of gender, textures, normal forces, and their interactions on the estimated coefficient of dynamic friction. The Bonferroni's t-test with $\alpha = 0.05$ (Morrison 1983) was used to evaluate the differences in the μ_k's between male and female subjects in this study.

Results

Kinetic coefficient of friction

Table 1 lists the mean and standard deviation of kinetic coefficients of friction for male and female volunteers of this study. The mean kinetic coefficient varies depending on the level of normal force and the type of texture. For males, the mean kinetic coefficient ranged from 0.73 (Test plate III, 10 N) to 2.05 (Test plate IV, 1 N), while for females, the mean kinetic coefficient ranged from 0.77 (Test plate II, 10 N) to 2.13 (Test plate IV, 1 N). The standard deviation of the kinetic coefficient ranged from 0.02 to 0.89 for male subjects and from 0.11 to 0.58 for female subjects, respectively. There are some minor differences in the mean kinetic coefficients of friction between male and female subjects. The largest absolute difference in kinetic coefficients of friction between the male and females subjects was 0.72 (Test Plate IV-5 N) and the smallest absolute difference was 0.02 (Test Plate I - 10 N). However, the gender difference in the measured kinetic coefficient of friction was not statistically significant, $F = 2.01$ and $p > 0.05$.

As there was no significant gender difference, we pool the male and female data together. Figure 5 plots the overall mean kinetic coefficients of friction of the six subjects under twelve test conditions, i.e., three levels of normal force and four types of texture. The results also suggest that both the texture of the surface and the exerted normal force affect the measured kinetic coefficients of friction. Under all three levels of normal force, test plate IV always yielded the largest kinetic coefficients of friction followed by test plates I, II, and III. The overall mean kinetic coefficient of friction ranged from 0.78 (10 N force on test plate III) to 2.09 (1 N force on test plate IV). The difference in the mean kinetic coefficient of friction due to texture of the test plates is statistically significant ($F = 31.54$, $p < 0.05$). However, there is essentially no difference in the mean kinetic coefficients of friction between test plates II and III for all three levels of force.

The results also indicate that there is a decreasing trend in the mean kinetic coefficients of friction as the exerted normal force increases. On the average, as the force increased from 1 N to 10 N, the mean kinetic coefficient of friction decreased from 1.42 to 0.94, a difference which is statistically significant ($F=6.83$, $p < .05$).

There was also a significant interaction effect due to texture and force level ($F = 3.29$, $p < .05$). The differences in the mean kinetic coefficients of friction among test plates were much greater for the 1 N force condition than for the other two force conditions. For the 1 N force condition, the biggest absolute difference in the mean kinetic coefficients of friction between test plates was 1.16, while for the 10 N force condition, the difference between plates in mean kinetic coefficients of friction was 0.39.

Finger Contact Area and Pressure

The gender difference in tip pinch strength was statistically significant, $t = -2.87$, $p < 0.05$. While the tip pinch strength of male subjects had were 73.6 N (SD: 11.5 N), the mean tip pinch strength of female subjects was 49.1 N (SD: 9.3 N). There was also significant gender difference in the palmar pinch strength, $t = -7.98$, $p < .05$. The palmar pinch strength of male subjects had a mean of 111.4 Newton and a standard deviation of 8.0 Newton. The palmar pinch strength of female subjects had a mean of 71.5 Newton and a standard deviation of 3.2 Newton.

Females of this study seemed to have finger contact areas larger than that of male subjects. For females, the nominal finger contact area while exerting 1 N normal force had a mean of 98 mm^2 and a SD of 39 mm^2. As the normal force increased to 5 N and 10 N, the mean nominal finger contact areas increased to 155 mm^2 (SD: 29 mm^2) and 226 mm^2 (SD 47 mm^2), respectively. For males, the nominal finger contact area while exerting 1 N normal force had a mean of 61 mm^2 and a SD of 24 mm^2. The mean nominal finger contact areas increased to 111 mm^2 (SD: 33 mm^2) and 175 mm^2 (SD: 69 mm^2), respectively, as the exerted normal force increased to 5 N and 10 N. The apparent gender differences in the nominal finger contact areas at these three normal force levels, however, were not statistically significant.

As a result, females in general experienced approximate a 3-fold increase (from 11.5 kPa (SD: 5.1 kPa) to 32.9 kPa (SD:5.8 kPa)) in the finger contact pressure as the exerted normal force increased from 1 N to 5 N. A ten-fold increase in the normal force, however, resulted in only a 4-fold increase to 45.7 kPa (SD: 10.9 kPa) in the contact pressure. Compared to female subjects, male subjects experienced less increase in the finger contact pressure. With 1 N normal force, the mean finger contact pressure was 18.3 kPa (SD: 8.0 kPa), while at 5 N normal force, the mean finger contact pressure was 48.2 kPa (SD: 16.1 kPa), an increase of about 2.5 times. With 10 N normal force, the mean finger contact pressure was about 66.2 kPa (SD: 33.9 kPa), an increase of about 3.5 times from that with 1 N normal force.

Overall, a 5-fold increase in normal force from 1 N to 5 N resulted in an increase of 3.5 times in finger contact pressure from 14.9 kPa (SD: 7.1 kPa) to 40.6 kPa (SD: 13.7 kPa). A 10-fold increase in normal force from 1 N to 10 N resulted in an increase of about 3.8 times in crease in the finger contact pressure to 55.9 kPa (SD: 25.2 kPa).

Discussion

No gender difference was found in the present study of the fingertip kinetic coefficients of friction on textured surfaces. Our finding of no significant gender effect seems to be consistent with the finding by Kennis (1994) in a study of fabric-to-skin friction. The results suggest that skin compliance may not be a significant determinant of kinetic friction of fingertip. Skin compliance measurements for males in Woodward's study were significantly lower than for females (mean two-point compliance: female = 2380.97 micron; male = 2088.14 micron; mean gap compliance: female = 1901.33 micron, male = 1528.21 micron). We did not measure in this study skin compliance in the way that Woodward (1993) did in his study. However, the results that the finger contact area of female subjects seems larger than that of the male subjects seemed to suggest that females' fingertips are in general more compliant than that of males. Nonetheless, the effect of such difference on the mean kinetic coefficients of friction seems minimal.

It is of interest to compare the normal finger contact areas of the Chinese subjects of the present study with that of the fourteen Caucasian male subjects in Bobjer et al's study of 1993. Bobjer et al. (1993) found the mean normal finger contact areas at 1 N and 10 N normal force were about 175 mm^2 and 250 mm^2, respectively. They were slightly greater than the 98 mm^2 and 226 mm^2 for the female subjects of this study, but much greater than 61 mm^2 and 175 mm^2, for the male subjects at 1 N and 10 N normal force. As the sample sizes of both studies were relatively small, it is premature to say that there was any definitively ethnic difference between Caucasian and Chinese in finger contact area or in finger compliance.

However, there seems to be no significant difference in the kinetic coefficients of friction reported in the study by Bobjer et al. (1993) and that found in the present study. For the Chinese male and female subjects of the present study, the kinetic coefficients of friction on textured surfaces were found to range from 0.79 to 2.09. The test plates in our study were directly adapted from four of the five test plates used by Bobjer et al. (1993). Thus, the results of the present study could be directly compared to that by Bobjer et al. (1993). As shown in Table 2, under similar test conditions, the mean kinetic coefficients of friction in the study by Bobjer et al. (1993) ranged from 0.74 to 2.22. There were minor differences in the kinetic coefficients of friction between these two studies. However, none of the differences were statistically significant based on the Bonferroni's t-test (Morrison 1983) at an alpha level of 0.05. Thus, ethnicity of the subjects did not appear to be a factor in the kinetic coefficients of friction.

Effect of surface texture and normal force on kinetic coefficient of friction
A negative relationship between the kinetic coefficients of friction and the exerted normal force was found in the present study. However, as seen in Figure 5, the negative correlation was more prominent when the surface of the test plate is either smooth (test plate IV) or with 75% of the area covered with ridge (test plate I) than when there is less ridge area. This is consistent with what others (Buchholz et al. 1988; Bobjer et al. 1993) have found regarding the frictional characteristics of human palmar skin: the human palmar skin does not follow the Amonton's laws of friction. Comaish and Bottoms (1971) measured the coefficients of static and dynamic friction between clean dry skin and sheet or knitted materials. They reported that skin obeys Amonton's laws of friction over a limited load range and this deviation may occur because skin is subject to viscoelastic rather than purely plastic deformation. As Bobjer et al. (1993) pointed out the frictional force of human palmar skin depends on the size of surface areas in contact with the skin and is not directly proportional to the normal force.

Human skin may have similar characteristics as the polymeric materials and thus behaves differently from the classical concepts of friction (Bobjer et al. 1993). As such, the kinetic coefficient of friction may vary not only with the surface contact pressure, but also with the sliding speed (Yamaguchi, 1990). In their study Bobjer et al (1993) controlled the speed of the finger across the test plates in the range 4.5 ~ 5.5 cm/s. In the present study, the sliding speed of the finger across the test plates was not controlled, but found to be in the range 0.6 - 3.8 cm/s. Nonetheless, the difference in finger velocity across the surface did not seem to affect the results, as evidenced by the insignificant difference in the kinetic coefficients of friction of the two studies.

There are limitations of the study. First, small sample size was used in this exploratory study. Only six subjects were studied. Second, none of the subjects had much experience in industrial activities requiring intensive use of hand tools. More studies of larger sample size with diverse industrial experience need to be conducted to identify relevant skin characteristics. Third, the textured and non-textured surfaces made of polycarbonate represent only a small fraction of the hand tool surface utilized in industrial environment. Other types of material such as aluminum and other types of textured surface should be used to characterize the frictional properties of palmar skin and hand tool surface and estimate hand force exertion in manual work. In addition to flat surface, the influence of curvature surface instead of flat surface on coefficient of dynamic friction should be further investigated. The effect of these factors on the coefficient of dynamic friction should be further evaluated to characterize the frictional properties between human palmar skin and hand tool surface.

Conclusions
This exploratory study characterized the frictional properties of the index fingertips of six Chinese, three males and three females, using a simple device. Three textured surfaces and one non-textured surface made of polycarbonate materials were used in this study to simulate the hand tool surface. Despite the simplicity in the design of the device, the kinetic coefficients determined in the study is similar to what other researchers have found. The kinetic coefficients of friction of index fingertip depend on surface texture and magnitude of the normal force exerted. There was no significant gender difference in the kinetic coefficients of friction.

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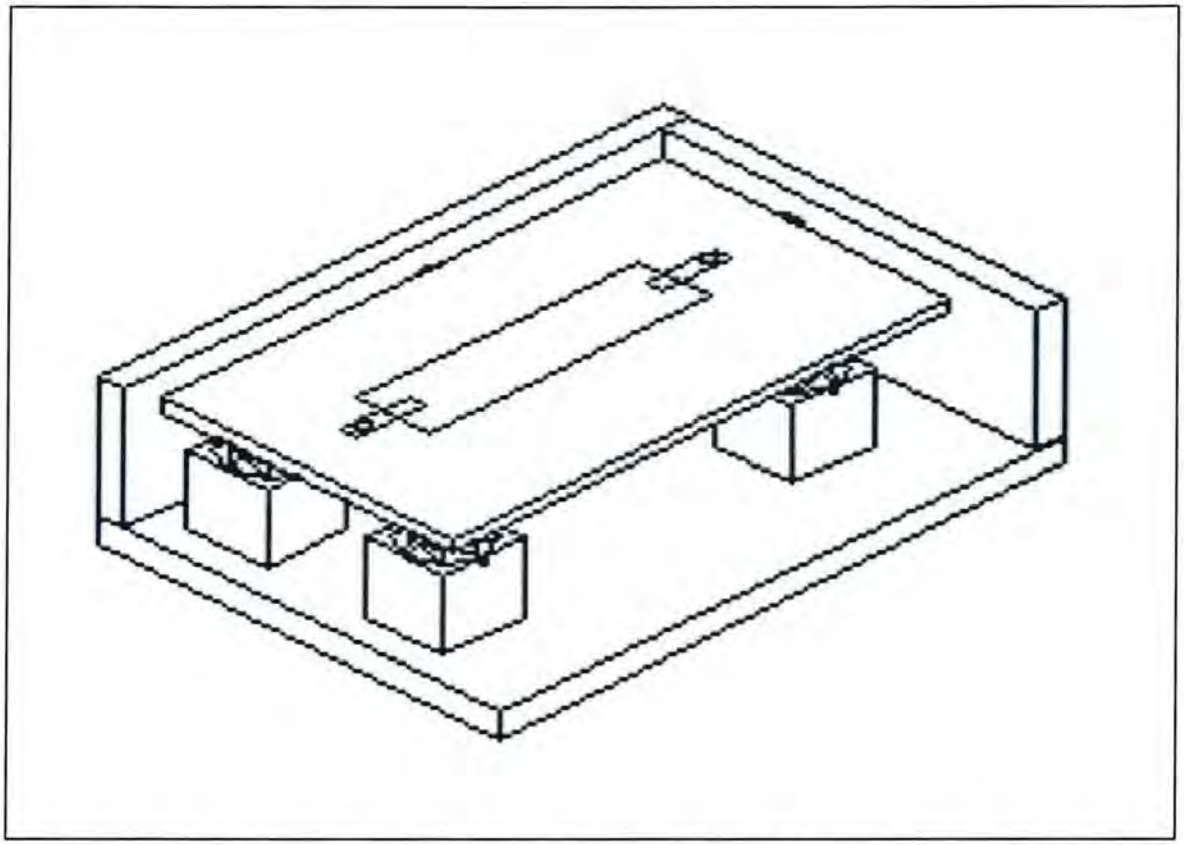

Figure 1. Experimental device for measuring the kinetic coefficient of friction

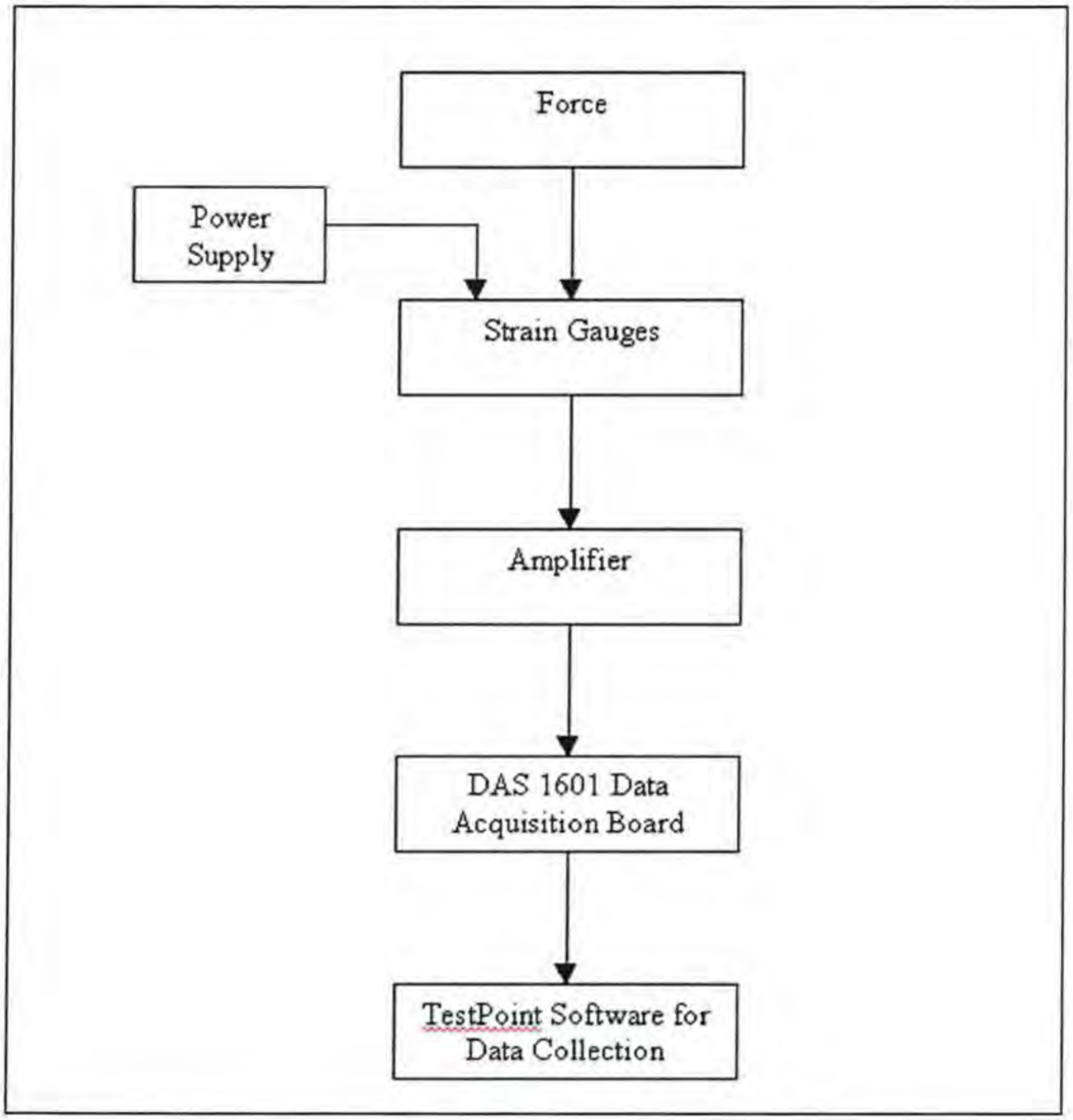

Figure 2. Block diagram of data collection system

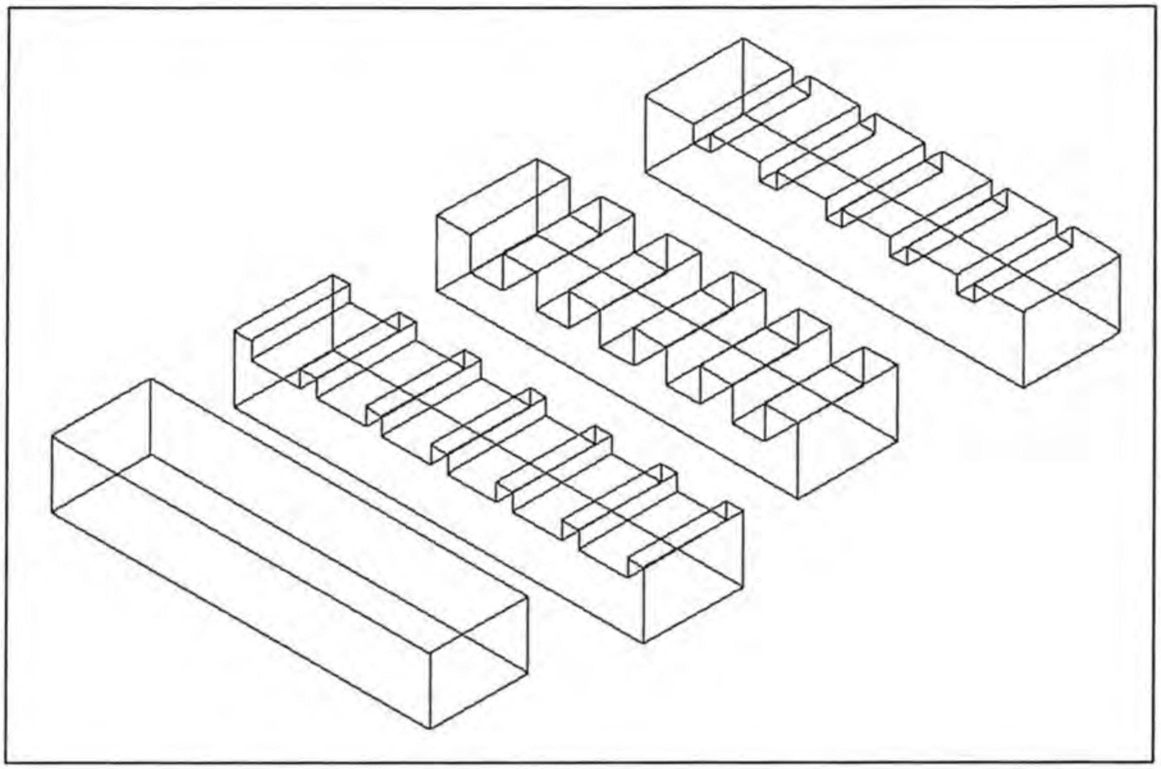

Figure 3. Configuration of textured and non-textured test plates

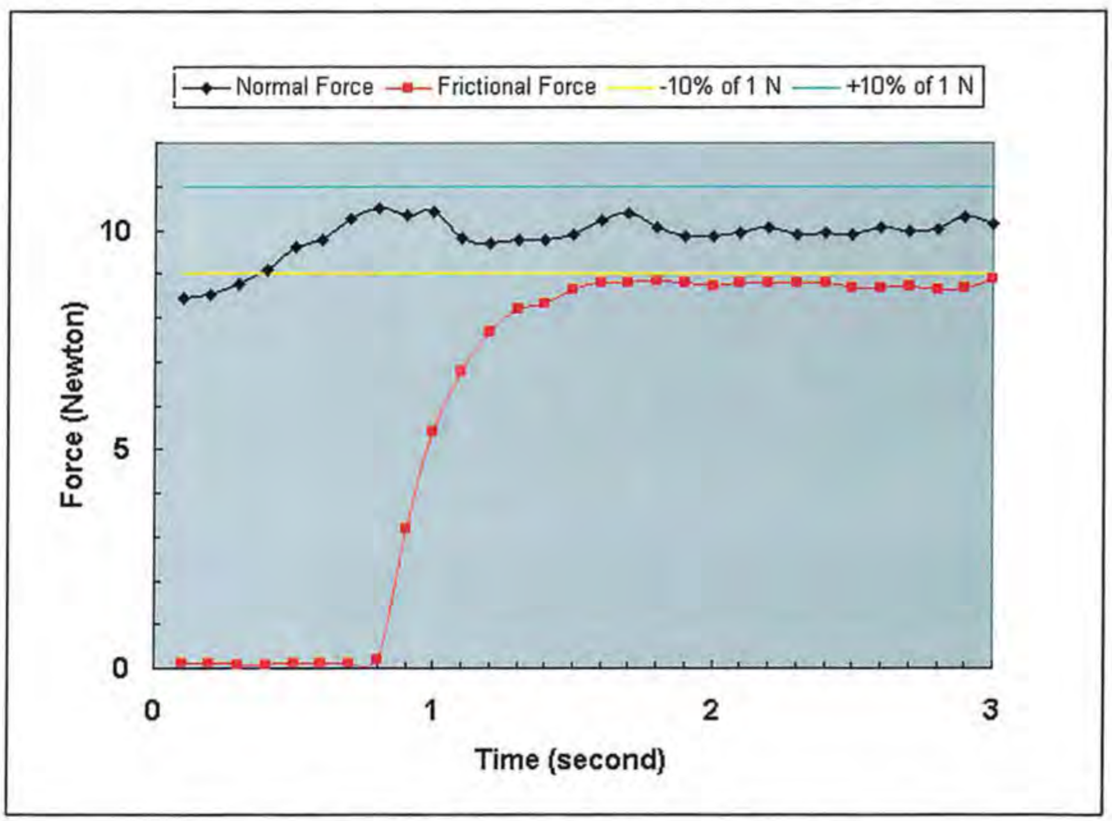

Figure 4. Sample of a typical measurement session

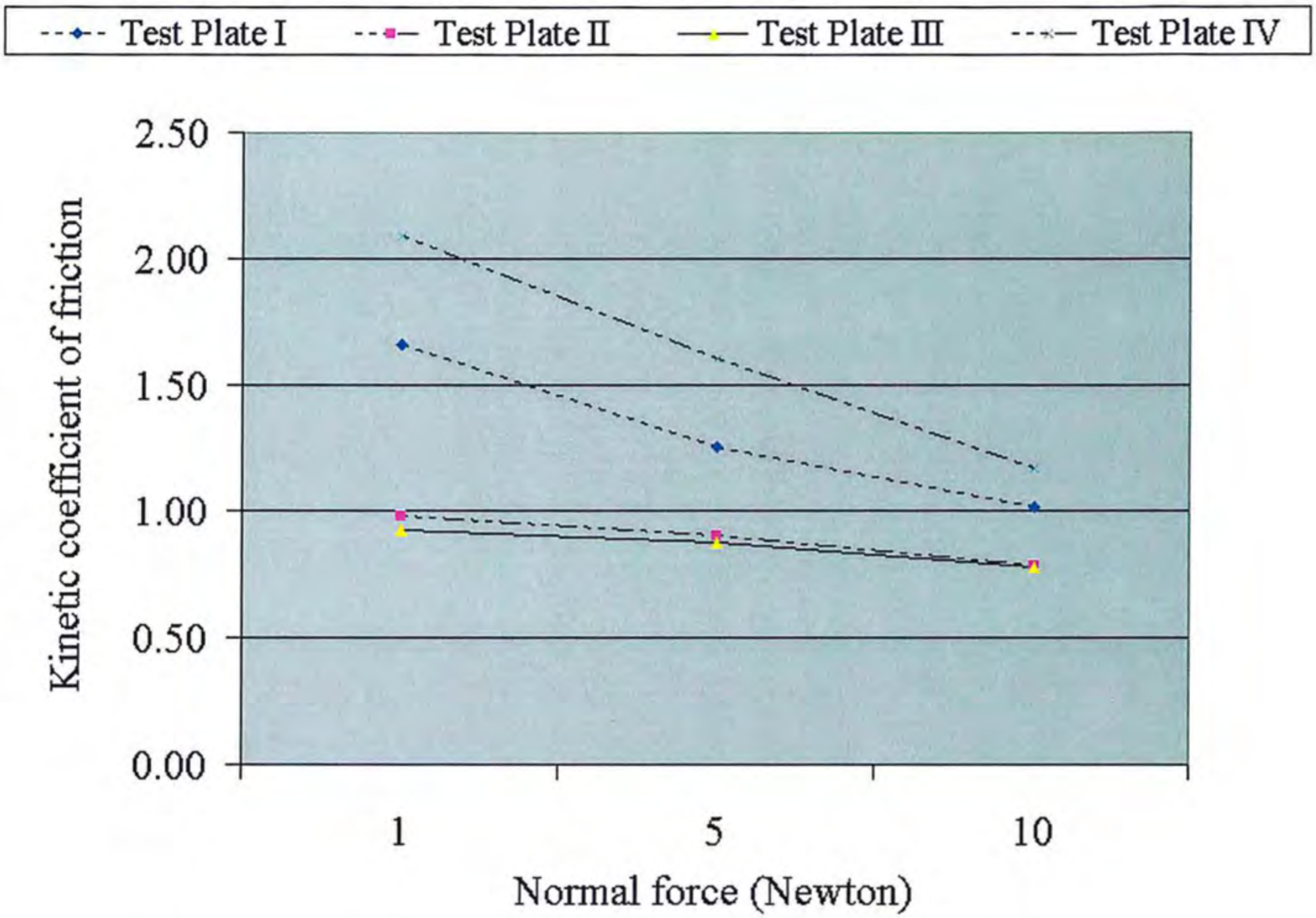

Figure 5. Overall mean kinetic coefficients of friction vs. texture and normal force

Table 1. Mean and standard deviation of kinetic coefficient of friction

Test Plate (% ridge area)	Normal Force (N)	Male Mean (Standard Deviation)	Female Mean (Standard Deviation)	Overall Mean (Standard Deviation)
Test plate I (75%)	1	1.61 (0.46)	1.70 (0.50)	1.66 (0.43)
	5	1.15 (0.40)	1.36 (0.12)	1.25 (0.29)
	10	1.03 (0.09)	1.01 (0.35)	1.02 (0.20)
Test plate II (50%)	1	0.96 (0.08)	1.00 (0.21)	0.98 (0.15)
	5	0.86 (0.02)	0.95 (0.20)	0.91 (0.14)
	10	0.81 (0.04)	0.77 (0.11)	0.79 (0.07)
Test plate III (25%)	1	0.82 (0.06)	1.04 (0.39)	0.93 (0.28)
	5	0.81 (0.05)	0.94 (0.20)	0.87 (0.15)
	10	0.73 (0.07)	0.82 (0.07)	0.78 (0.08)
Test plate IV (100%)	1	2.05 (0.89)	2.13 (0.58)	2.09 (0.67)
	5	1.25 (0.09)	1.97 (0.47)	1.61 (0.49)
	10	1.09 (0.12)	1.24 (0.08)	1.17 (0.12)

Table 2. Kinetic coefficients of friction: Present study vs. Bobjer et al. (1993)

Test Plate (% ridge area)	Normal Force (N)	Present Study Mean (Standard Deviation)	Bobjer et al. (1993) Mean (Standard Deviation)
I (75%)	1	1.66 (0.43)	1.44 (0.68)
	10	1.02 (0.20)	0.85 (0.19)
II (50%)	1	0.98 (0.15)	0.75 (0.30)
	10	0.79 (0.07)	0.74 (0.17)
III (25%)	1	0.93 (0.28)	0.79 (0.11)
	10	0.78 (0.08)	0.76 (0.03)
IV (100%)	1	2.09 (0.67)	2.22 (1.12)
	10	1.17 (0.12)	1.01 (0.35)

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A Real-Time Personal Heat Stress & Heat Strain Monitor in Protective Suit

Abstract

The goal of this study is to develop a real-time personal monitor capable of evaluating heat stress and heat strain encountered by workers wearing encapsulating protective clothing. This monitor simultaneously characterizes the climatic conditions of the microenvironment and the physiological responses of the worker in protective clothing. Specifically, the study (1) integrated temperature and humidity sensors to continuously characterize the microenvironment in a protective suit; (2) integrated heart rate sensors and body temperature sensors to characterize the physiological response of the person wearing a protective suit; and (3) tested the utility of two wireless transmitters, 0.9 GHz and 2.4 GHz, to transmit the heat stress and heat strain signals.

This study represents an innovative integration of information technology and sensor technology for hazard surveillance. In addition, this study has direct application to personal exposure surveillance of workers wearing protective suits and utility for the design of protective clothing.

Background

Heat stress is a well-recognized safety and health hazard especially for workers that have to wear protective clothing in their work (NIOSH, 1985, 1986). However, the exposure surveillance of heat stress for workers wearing protective suits is still limited to a general assessment of the marcoenvironment (Morris, 1995). An underestimate of the heat stress based on this general approach may result, and subsequently increase the worker's risk for head-induced illnesses and injuries. An overestimation of the heat stress and the resultant control measures may lead to a loss of productivity. It is more meaningful to evaluate the heat stress based on measurements taken in the microenvironment in the protective suit.

Workers may also differ in their bodily response, heat strain, to the heat stress. This difference in heat tolerance may be due to a variety of factors, such as acclimatization, age, and physical condition on a particular day. Identifying heat-intolerant individuals and providing real-time monitoring have been long recognized as important issues in need of research and development (NIOSH, 1986; Bernard and Kenney, 1994; Reneau and Bishop, 1996). Currently, there are at least three heat-strain monitors available commercially. The Questemp II (Quest Technologies, Inc.) measures only the tympanic membrane temperature, while the HS-3800 (Metrosonics, Inc.) measures the both heart rate and skin temperature. Another telemetric system (VitalSense by Mini-Miter Co., Inc.), capable of monitoring body temperature, heart rate, and activities, tends to be expensive and has not received wide acceptance in the field. These three monitoring instruments or systems may be useful for heat strain evaluation.

However, none of these commercially available personal monitors provides measurements of the microenvironment in the protective suit. Therefore, it is impossible to provide the data necessary for the establishment of a field-based relationship between heat stress and heat strain in the protective suit. There is a definite need for a real-time, personal monitor to evaluate heat stress-heat strain for worker in a protective suit.

It is the goal of this study to develop a real-time personal monitor capable of evaluating heat stress and heat strain encountered by workers wearing encapsulating protective clothing. The monitor consisting of 5 sensors and two transmitters will be a valuable tool for the purpose of exposure surveillance and biological monitoring. In addition, the monitor will allow the collection of field data necessary not only for addressing the research needs identified by the National Institute for Occupational Safety and Health (NIOSH, 1986) but also for potential design modification of protective suits.

The real-time personal monitor developed in this study is capable of evaluating heat stress and heat strain encountered by workers wearing encapsulating protective clothing. This monitor simultaneously characterizes the climatic conditions of the microenvironment and the physiological responses of the worker in the protective clothing.

Specifically, the study (1) integrated temperature and humidity sensors to continuously characterize the microenvironment in a protective suit; (2) integrate heart rate sensors and body temperature sensors to characterize the physiological response of the person wearing a protective suit; and (3) tested the utility of two wireless transmitters, 0.9 GHz and 2.4 GHz, to transmit the heat stress and heat strain signals.

Methods

As shown in figure 1, the conceptual design of the heat stress and heat strain monitor consists of two sets of sensors, transmitters and receivers. The first set of sensors and transmitters is for the measurement of physiological responses and consists of two thermistor probes (Sensor Scientific, Inc.), one for chest skin temperature and one for tympanic membrane temperature, and one heart rate monitor (Polar, Inc.). The signals from these three sensors are transmitted through transmitter #I to receiver #I.

The second set of sensors and transmitters is for heat stress surveillance based on the measurement of the climatic condition inside the protective suit. This set of sensors and transmitter is composed of one thermistor for temperature and one sensor for relative humidity (Vernier Software, Inc.) and a transmitter. Signals from both sensors are transmitted through transmitter #2 to receiver #2. Methods for real-time data collection depend on the type of wireless transmitters.

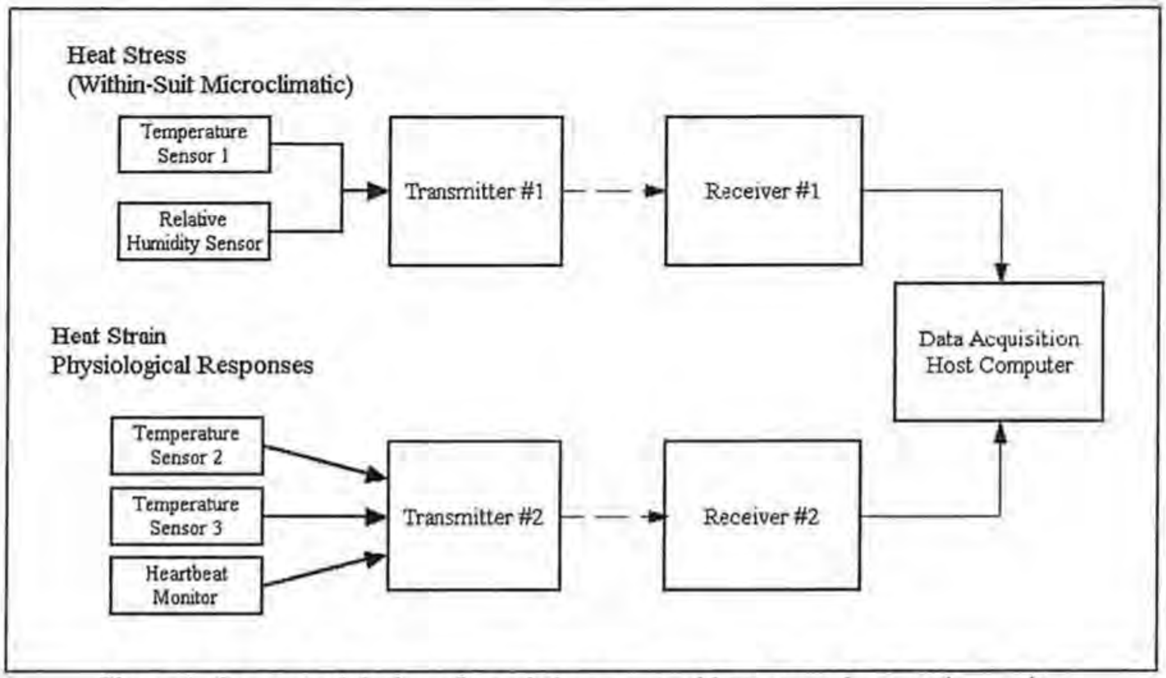

Figure 1. Conceptual design of a real-time personal heat stress-heat strain monitor

Temperature Measurement

Thermistor probes were used to measure the temperature of the air inside the protective suit and of the human body probe.

Humidity Measurement

Relative humidity (RH) was measured using a sensor purchased from the Vernier, Inc. As this RH sensor is sensitive to light and electrostatic discharge, the sensor was encased in a box specially built in the laboratory. The RH sensor responds to the humidity change by changing its output voltage with a range from 1.023 V to 3.821 V for 0% and 100% RH, respectively. The RH reading from the sensor was verified using a sealed chamber containing either desiccant or water to control the humidity inside at 0% and 100% RH. Another digital humidity sensor (Humidiguide 5566) used as a reference sensor was also placed in the chamber.

As the RH sensor has a response time of more than 60 minutes, it was necessary to fit the housing of the sensor with a miniature, 5-volt DC brushless fan to create sufficient air movements. The resultant housing for the RH sensor was of a dimension of 1.5" x 1.5" x 1.5". Using the 5V micro-fan in a non-transparent box, the response time came down to less than three minutes in the extreme situation. However, the response time was less than a minute for a typical environmental condition, i.e., from 100% RH to about 50% RH.

The 0.9 GHz transmitter has a maximum input value of 1.5 V and the RH sensor gives a maximum output signal of 3.82 V. Therefore, additional resistors, 2-M ohms and 1-M ohms, were placed between the RH sensor output and the 0.9 GHz transmitter to reduce the input signal to the 0.9 GHz transmitter. These resistors were selected to match the internal impedance of the

RH sensor. With this configuration, three levels of RH, i.e., 0%, 53% and 100%, were tested to establish a calibration line.

Heart Rate Measurement

The heart rate (HR) monitor (Polar, Inc.) is composed of two components, a transmitter belt and a receiver. The transmitter detects each heartbeat through two electrodes with ECG accuracy and transmits the heart rate information to the receiver with the help of a low frequency electromagnetic field. For each heartbeat detected, the HR monitor's receiver receives the transmission, and passes a 3V pulse. The reception range between the HR monitor's transmitter belt and its receiver should be less than 3 feet, as recommend by the manufacturer.
In this study, the receiver was placed by the forehead and was within 1-foot distance of the transmitter belt. The reading of the HR monitor was compared to manual counting of the pulse at the common carotid artery of the neck for a minute.

Transmitter Test

Two types of transmitters were tested in this study. One transmitter (MicroStrain, Inc.) transmits digital signals at a frequency of 0.9 GHz, and the other transmitter (RF-Link, Inc.) transmits analog signal at 2.4 GHz. The 0.9 GHz transmitter is powered by a 9-volt battery and is capable of transmitting five sets of digital signals. The 2.4 GHz transmitter is powered by a 12-volt battery and is capable of transmitting simultaneously two sets of analog signals with switching among four channels.

Both transmitters require receivers. The 0.9 GHz transmitter uses a receiver that transmits real-time digital signals through an RS-232 communication port to a personal computer. Transmission of the data is controlled by an MS-DOS (Microsoft Disk Operating System) software provided by the vendor.

The 2.4 GHz uses a receiver that transmits the analog signals and therefore requires an additional analog/digital data acquisition board for data collection. In the present study, the 2.4 GHz receiver was connected to a data acquisition system consisting of an A/D converter (DAS 1601, Keithley, Inc.) controlled by an application program written in-house with TestPoint software package (ADAC Corp.).

The sampling rate of the 0.9 GHz transmitter was set at 100 Hz, while the sampling rate of the 2.4 GHz transmitter is only limited by the A/D acquisition board and the number of channels (up to16 channels) used. A computer equipped with a Pentium 100-MHz processor was used for data collection.

Statistical Analysis

Correlation and regression analyses were conducted to evaluate the correlation between two sets of measures of a specific parameter, e.g., thermistor probe's resistance readings vs. temperature reading of the mercury thermometer, and to establish a calibration line. Analysis of variance was used to evaluate the differences between thermistors. All statistical analysis was conducted using a personal computer with statistical analysis procedure in the Microsoft Excel spreadsheet.

Results

Temperature Sensor

Temperature Sensor Using the 0.9 GHz transmitter

Figure 2 shows the thermistor probes' readings collected through the 0.9 GHz transmitter. The transmitted digital signal is represented as an averaged digital reading. The R-squared value of the regression line was greater than 0.999 ($p < .001$). The regression line for calibration was determined to be: Temperature (°F) = 0.002825 (Digital Reading) + 10.69617 to be: Temperature (°F) = 0.002825 (Digital Reading) + 10.69617

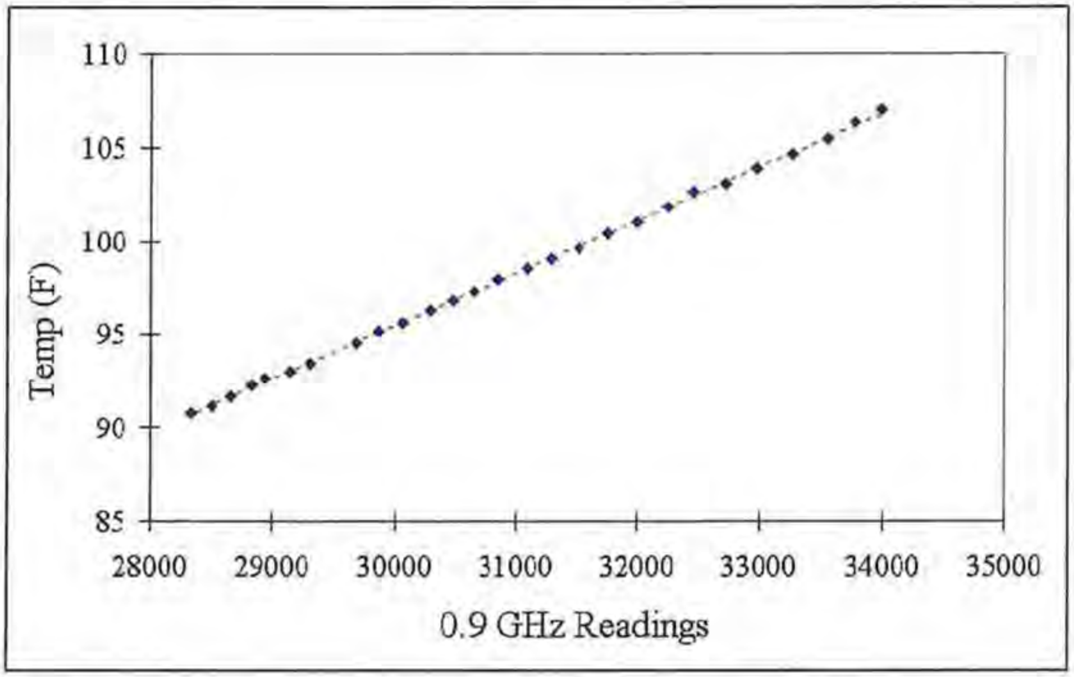

Figure 2. Thermistor probe temperature readings transmitted through a 0.9 GHz transmitter.

Multiple-Channel Temperature Measurement Using a Whetstone Bridge

Additional tests were conducted to verify the responses of three thermistors used in the present study. This was done to determine the variation among thermistors. Three thermistors were simultaneously inserted into a beaker full of water at temperature ranging from 100.2 °F to 104.3 °F. Consistent results were found with these three thermistor probes. There was no statistically significant difference among the thermistors.

Temperature Measurement of Multiple Thermistors Using the 0.9 GHz Transmitter

There were differences, not statistically significant, among the thermistor probes if the data were transmitted through a Whetstone bridge and the 0.9 GHz transmitter.

Relative Humidity Sensor

RH Measurement using the 0.9 GHz Transmitter

Figure 3 shows the RH calibration data. The R^2 value of the correlation and regression analysis was 0.998 ($p < 0.05$). The regression equation for RH is as follows:

Relative Humidity (%) = 0.00723 (0.9GHz Transmitter reading) - 276.7

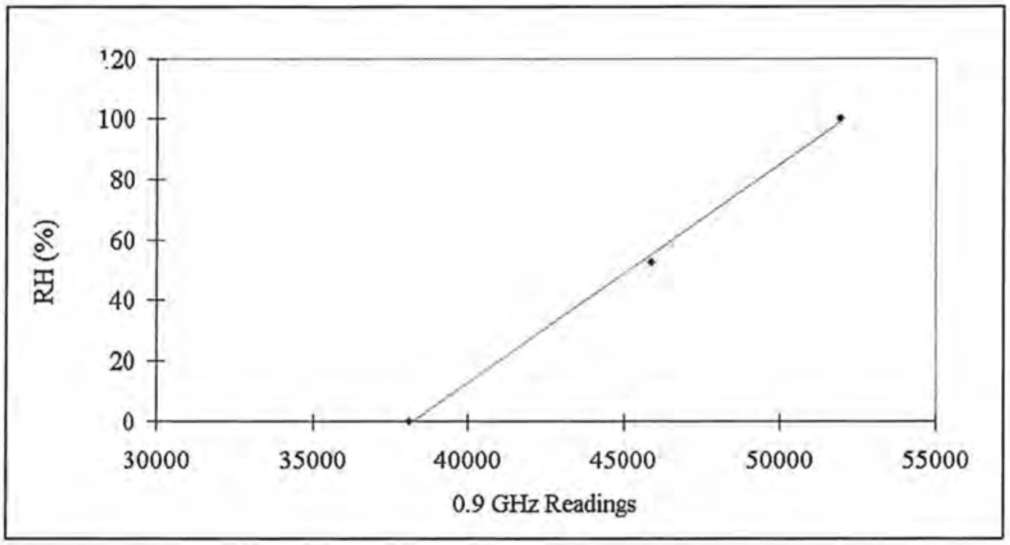

Figure 3. Relative humidity calibration with signals transmitted through a 0.9 GHz transmitter.

RH Measurement Using 2.4 GHz Transmitter

The 2.4 GHz transmitter in its current configuration can only takes AC peak-to-peak signal of 1 V. Since the RH sensor output signal is a DC signal varying between 1.2 V to 3.8 VDC, it can not be used with the 2.4 GHz transmitter.

Heart Rate Monitor

Heart Rate Measurement Using Analog/Digital Converter

Figure 4 shows the heart rate data collected with the HR monitor using an A/D converter and that obtained with manual pulse counting. The heart rate measured ranged from 76 beats/min to 123 beats/min. The correlation between the two was, an R^2 value of 0.999 ($p < .001$).

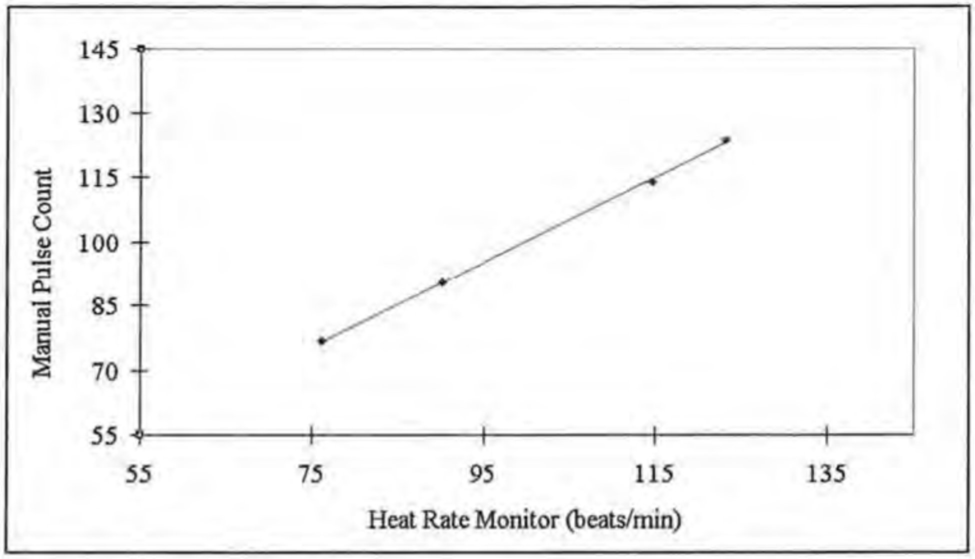

Figure 4. Manual pulse count vs. heartbeat monitor count

Heart Rate Measurement Using the 0.9 GHz Transmitter

The results of the study indicate that the HR monitor signal can be used directly with 0.9 GHz transmitter. Figure 5 shows a sample of the data collected and the correlation coefficient was greater than 0.99.

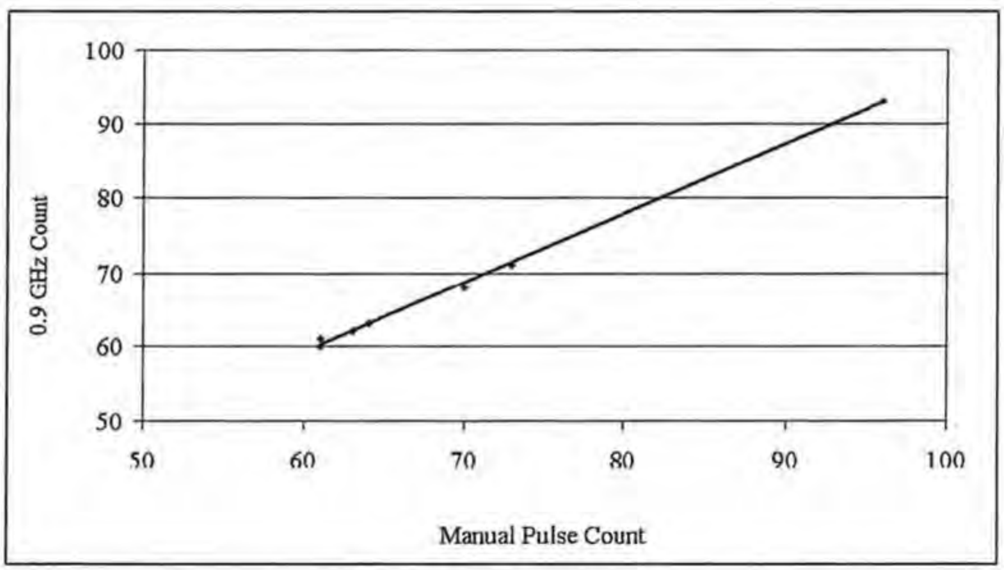

Figure 5. Manual heartbeat count vs. heartbeat monitor count transmitted through a 0.9 GHz transmitter.

Heart Rate Measurement Using 2.4 GHz Transmitter

Heart rate ranging from 62 to 120 beats/minute was tested with the heart rate monitor. Compared to the pulse sensed with fingers, occasionally there were only one or two miscounts, as shown in Figure 6.

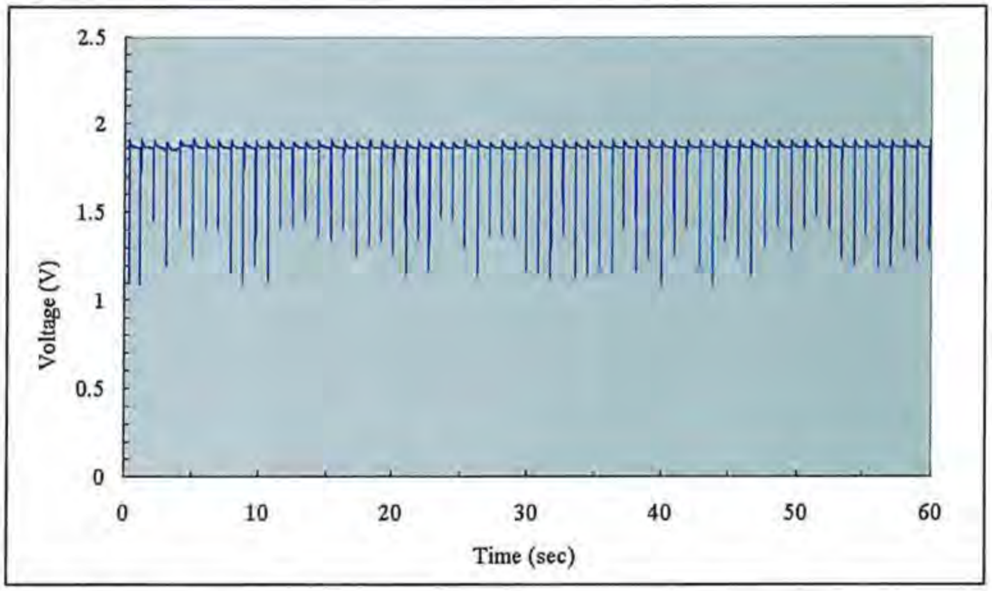

Figure 6. Heartbeat signals received from a 2.4 GHz transmitter.

Discussion

This study evaluated the feasibility of integrating thermistor temperature probes, a relative humidity sensor, and a heart rate monitor, with wireless transmitters for the surveillance of both heat stress and heat strain. The results showed that while some of the sensors, such as the thermistor temperature probes, functioned satisfactorily and could be used without modification for the surveillance of heat stress and heat strain, others required additional modification for the purpose of hazard surveillance.

For example, the thermistor probes used in the present study were calibrated in the laboratory between 32 °C and 42 °C. High correlation, $R^2 > 0.99$, was found between the temperature measured with a mercury thermometer and the derived temperature reading based on the resistance change of the thermistor. Inter-day and inter-thermistor variability has also been evaluated and found to be minimal. The results also showed that heartbeat monitor also performed as expected. Each heartbeat at a rate from 60 beats/minute to 120 beats/minutes was clearly discernible during laboratory tests.

As for relative humidity measurement, the sensor needs modification to shorten the response time. The response time of the sensor in its original design is too long. However, the response time of the sensor was reduced to less than a minute by adding a small, brushless fan for increased air circulation. The modified sensor-fan design performed satisfactorily in the controlled laboratory settings. Calibration line at 20 °C for three relative humidity levels, $R^2 > 0.99$, was established. Concordance with another digital humidity sensor gave satisfactory results.

The test results of two wireless transmitters, operating at 0.9 GHz and 2.4 GHz, respectively, showed that each transmitter has its advantages and disadvantages. While the 0.9 GHz transmitter can easily transmit signal from the thermistor probes and heartbeat monitor, it can not take the signal directly from the humidity sensor. As for the 2.4 GHz, while it can transmit the heartbeat signals in its current configuration, it does need an additional transducer to transmit the signal from the relative humidity sensor. In this study, we have built a simple oscillator circuit that allows the transmission of relative humidity sensor's signal.

Based on the results of the present study, the design of the real-time personal monitor for heat stress and heat strain would consist of three thermistor temperature probes, a relative humidity sensor, a heart rate monitor, one 0.9 GHz and one 2.4 GHz wireless transmitters. The 0.9 GHz transmitter will be used to transmit signals from the three thermistor probes. One thermistor probe will be used for air temperature and the other two thermistor probes will be used for body temperature, measured either at skin surface of different location or at the mouth or in the middle ear.

More tests and developmental work should be conducted to optimize the design of the real-time personal heat stress - heat strain monitor. One consideration is the cost. While the 2.4 GHz transmitter costs less than $200 a pair, the 0.9 GHz transmitter and receiver set costs more than $1,500. To reduce the cost of the real-time heat stress - heat strain monitor, it is preferable to use the 2.4 GHz transmitter. However, it would require the conversion of DC signals from the temperature sensor to AC signal and a remote, automated channel switch. The is due to the fact that the 2.4 GHz transmitter/receiver in its current package only accepts AC signals and allows the transmission of two sets of signals on one channel at a time, despite of the four channels available. Our laboratory is working on building an inverting amplifier so that all sensors could be connected directly to the 2.4 GHz transmitter and receiver.

Conclusion

This study demonstrated the feasibility of integrating sensor technology and wireless transmission technology for the heat stress and heat strain surveillance in the defense / nuclear industry. This real-time heat stress - heat strain monitor is not only useful as a research tool to elucidate the relationship between heat stress (within-suit microclimate) and heat strain but also of great utility for exposure surveillance in the field.

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5. Evaluation of current exposure and medical surveillance programs at Los Alamos and Lawrence Livermore National Laboratories

To evaluate the medical and exposure surveillance programs at LANL, identify discrepancies between health and safety "needs" and established monitoring programs, and develop an integrated surveillance system that efficiently combines hazardous-exposure, biological, and health-outcome monitoring of the worker population.

Abstract

We assessed whether medical and industrial hygiene exposure monitoring information routinely collected at nuclear facilities such as the Los Alamos National Laboratory (LANL) are useful screening tools to help predict long-term health outcomes and would allow to conduct epidemiologic research to assess health effects in current and former nuclear workers from exposure to mixtures of chemicals and radiation.

First, we found that medical records did not systematically collect job location, job history, and job title information. A pilot study of machinists revealed that no other records existed or could be made available to us that would have allowed us to link medical test results to information from industrial hygiene area sampling data and/or other exposure-related data bases maintained by the Environmental Health and Safety department.

Second, we linked three large LANL databases: 1) noise sampling data; 2) hearing conservation data, and 3) audiometric testing data in order to examine the effectiveness of the hearing conservation program (HCP). We found that due to the inherent lack of worker location and job history data it was impossible to assign available noise level measurements for work areas to individual workers. We analyzed data for a small group of workers for whom individual noise measurements existed and saw a clear relationship with duration of exposure, noise levels, and 'intermittent' noise. If these databases were maintained in a manner that would allow to link outcome (audiometry) data for workers to area noise measurements, they would be of great use for future and continued evaluations of the HCP and hearing loss prevention measures.

Finally, we used data collected by the occupational physician of the Fernald nuclear facility and documented in CEDR to evaluate the effect of combined exposure to chemicals and radiation on cancer mortality in nuclear workers. We combined an extensive chemical exposure data set with mortality files and radiation data provided in CEDR and investigated whether and to what extent the different and multiple chemical exposures contributed to the mortality experience of Fernald

workers. The results of these analyses have been documented in two publications attached to this report.

Introduction

The goal of the epidemiologic component of this 'hazard surveillance in the nuclear industry' project was to assess whether medical information routinely collected for medical surveillance and exposure information collected during industrial hygiene exposure monitoring at nuclear facilities such as the Los Alamos National Laboratory (LANL) could be used to:

(1) assess whether routinely collected medical data allows us to predict long-term health outcomes, i.e. can be used as a screening tool;
(2) evaluate the effectiveness of medical surveillance programs with regard to prevention of chronic occupational diseases;
(3) whether data from both medical and industrial hygiene surveillance could be used to aid epidemiologic research and help us assess long-term health effects in current and former nuclear workers due to exposure to mixtures of chemicals and radiation.

Dr. Ritz and her graduate students visited LANL several times during the course of this project and established collaboration with members of the medical group, specifically with Drs. Williams, Smith, and Wiggs. The main goal of these visits was to gain an overview over past and current medical surveillance strategies employed at the laboratory, to identify information that would allow us to assess LANL's medical surveillance needs, and to determine how epidemiologic methods could be employed to evaluate program effectiveness and gaps. Specifically, we expected that epidemiologic tools should be able to help improve the effectiveness of medical surveillance and aid efforts to prevent chronic diseases of occupational origin. Originally, we had proposed to target the following diseases: cancers, musculo-skeletal diseases, and neurologic/ neuropsychiatric disorders. However, in the course of the project it became necessary to shift our focus to the outcome 'hearing loss', a chronic sensori-neuronal disorder. The reason was that no data was available at LANL that would have allowed us to collect information about the occurrence of the former diseases/disorders among LANL workers in a systematic manner i.e. beyond collecting singular case reports (see also our pilot project results below).

In order to evaluated whether medical data routinely collected at the LANL facility might be useful for the detection of early symptoms of occupationally related diseases and, thus, be potentially useful as screening devices, workers needed to be systematically followed to assess longer-term health outcomes. Problems preventing us from conducting long-term follow-up of employees at LANL - even within small defined subsets of workers - are described exemplary in our pilot case study of a cluster of machinists diagnosed with elevated liver-enzymes in the late 1980s (see below). In addition, since LANL medical records did not systematically collect job location, job history, and job title information we were unable to link medical test results to information from industrial hygiene area sampling data and/or other exposure-related databases maintained by the Environmental Health and Safety (EHS-2) department. We were also unable to find a database providing worker location information that would have allowed us to link worker medical records to industrial hygiene area sampling for chemicals.

Thus, after completion of the LANL machinist pilot project (see below) we decided to proceed with the following two projects to achieve goals 2) and 3) formulated above. We:

(1) evaluated the effectiveness of the hearing loss prevention program at LANL, since for this chronic sensori-neuronal disorder we were able to obtain systematic outcome information for LANL workers;

(2) used data collected and documented by the occupational physician of the Fernald nuclear facility to evaluated the effect of combined exposure to chemicals and radiation on cancer mortality in nuclear workers.

In the following we will first describe and make some recommendations concerning the LANL medical and industrial hygiene surveillance programs. Second, we will report the results of our machinist pilot project, followed by a brief report of results from our Fernald nuclear worker mortality study (publications are included into this report). Last, we will present our evaluation of the LANL hearing loss prevention program.

Medical Surveillance at LANL

The medical surveillance at the LANL focuses on surveillance required by regulations and certification programs such as human reliability tests required for firefighters and for workers using respirator equipment as well as 'fitness for duty' exams. LANL-UC employees are invited to medical examinations in 1-, 2-, and 4-year intervals, depending on age and membership in 62 surveillance or certification categories (see attached list 1, attachment). Depending on which surveillance category a worker qualifies for, exams include any of 26 routine medical tests (see list 2, attachment). The only chemical for which biological monitoring data is routinely collected is blood lead.

The medical staff performs between 5,000 and 6,000 exams annually. Every LANL employee is invited for new-hire, work-termination, and possibly some periodic exams. While the new-hire exam is required by laboratory policy, termination exams are required only for a subgroup of employees, and periodic exams can only be offered when the medical department has the capacity to perform medical exams apart from those required. Employees are free to deny the offer of non-required exams. Members of the medical department felt that the acceptance rate for periodic exams decreased due an increased participation of the occupational medical facility in drug- and alcohol-screening programs which created some reluctance to accept non-required medical benefits.

Employees who return from sick leave after more than five days are required to be examined by occupational medicine staff before they are allowed to return to work. Shorter absences are not documented in the files of the occupational medicine department. Medical histories and test results are recorded in a standardized manner and retained almost exclusively in hardcopy format in employee's files. For some medical test procedures, such as audiometry tests, computerized data are available.

Furthermore, the medical department also offers human reliability exams and drug testing and new-hire and termination exams to employees of the two main subcontractors at LANL (1500 craft employees and about 500 professionals). An arrangement has been made to report all on-the-job injuries and illnesses of subcontractor employees to the occupational medicine department as well.

Recommendations
We strongly recommend that all medical test results are stored with a personal identifier and are available in computerized format.

Industrial Hygiene Surveillance at LANL
It is the task of the industrial hygiene/health and safety group at LANL to identify and refer employees for inclusion in any of the medical surveillance programs. The UCLA team learned that in the early 1990s LANL began to integrate the medical and industrial-hygiene systems. Some of these efforts were required by the Laboratory's UC contract as well as by DOE-orders (DOE 5480.8A, 5480.10, 5480.4, 5483.1A) and enhanced by a peer-review process involving all three UC Laboratories (Berkeley, Lawrence Livermore, LANL). They were initiated in 1993 and focused on a medical and industrial hygiene interface to integrate data across the two systems, i.e., across the medical and exposure surveillance databases.

The industrial hygiene group at LANL created databases to be integrated into a "health-hazard-assessment" (HHA) system. The HHA system is based on operation code data, an assessment of the types of chemicals used, the expected dose (which might depend on vapor pressure and particle size etc.), the duration and frequency of exposure, toxicity, and an evaluation of whether protective control measures are non-existent, effective or non-effective. Also, different from other systems previously used this system systematically collects personal identifiers for all workers involved in operations and processes evaluated. A final score based on all of the collected IH-data guides the development or improvement of protective controls and/or medical surveillance activities.

The content of the HHA system is based on general criteria previously established by IH to evaluate work place hazards. Nevertheless, previously field notes have been kept as individual documents. Since they were not sufficiently standardized, they provided only a fragmented view of hazards in the workplace. Furthermore, these documents were not available to medical-care providers and, thus, could not be used as a guide to potential health hazards encountered by employees in the work place.

The main databases (first established in 1993) that contributing to health hazard assessment at LANL are:

- An automated chemical inventory system (all chemical substances for which Material Safety Data Sheets (MSDS) exist). This database is linked to procurement and allows the industrial hygienist to know which chemicals are bought and used at the facility. A 1991 baseline inventory of chemicals is regularly beingupdated. The system is further fed by annual reconciliation updates that tracks movement of containers once each year and chemical disposal records. This system tracks about 250,000 containers (95% of all chemical containers at the facility), of which 170,000 are in active use.
- A second database contains information on carcinogens only. This database identifies individual employees who use each carcinogen and the processes in which they are used. The

list of chemicals is periodically reviewed and changed according to changes in the use of chemicals at the facility.
- An on-line database of MSDS information obtained from a commercial vendor.
- An operation code database that identifies tasks and processes with a hazard component and a list of employees involved in each task or process. This database relies on industrial hygiene-field work and facility walk through to identify the necessary information. This database will include exposure information about personnel hired by subcontractors as well.
- OSHA 200 log information on workplace injuries and illness (excluding detailed medical information).
- An occupational exposures sampling databases containing information on location, substance, test result, and possibly personal identifiers of the sampled employees.

Recommendations
This computerized HHA system when available to medical-care providers will aid medical surveillance efforts at LANL by providing an instant guide to potential health hazards in the work place. If the information is not only available for active employees, but stored it could aid epidemiologic exposure assessment efforts in an unprecedented way by providing personal exposure information for workers over long periods of time. Unfortunately, the system was not yet functional when we conducted this hazard surveillance project and thus could not be evaluated.

Pilot project: a case study of machinists at LANL
The limited budget available for the epidemiologic evaluation of medical surveillance as part of this hazard surveillance project precluded extended data-collection efforts at the facility. Thus, during our first visits to the LANL facility, we decided that it was necessary to conduct a pilot epidemiologic evaluation project that would allow us to identify all data resources available – possibly in computerized format - to track past and current workers at risk of chronic health problems, and to develop a plan for evaluating the success of established routine medical-surveillance procedures.

At one of the first meetings with the medical staff at LANL, we identified two areas that needed attention: 1) potential chronic neurotoxic effects due to solvent use in machining operations; and 2) potential musculoskeletal disorders caused by the insufficient ergonomic design of glove boxes used at the facility. We agreed to concentrate on the medical and epidemiologic surveillance of neurotoxic effects, since Dr. Liu (UCLA) was responsible for the ergonomic analysis of glove-box work as part of this grant.

The question of long-term neurotoxic effects from machining operations was raised first when a former machinist was diagnosed with an organic brain syndrome. The occupational physician who examined this worker recalled the case of another machinist who several years prior to this event had complained of chronic sleep disturbances. Furthermore, the physician recalled that a group of machinists showed elevated values for several liver enzymes during routine medical exams in the late 1980's. Some machinists who had tested positive were re-tested for liver enzymes elevations 6 weeks after the first positive result, and others were also examined by an outside gastro-enterologist. However, the occupational medicine department was unable to conduct a systematic investigation into the causes of this cluster of workers with abnormal liver function because at that time it occurred the machining department was undergoing major changes and many machinists were transferred to other departments. Three cases of chemically related hepatotoxicity were diagnosed in this group.

The increased liver enzymes may have been precursors of chronic neurotoxic effects induced by solvent use. In addition, occupational medicine noted that most of the older machinists were wearing hearing aids, although they had been included in a hearing-conservation program for more than a decade. The hearing loss experienced by machinists might be influenced by neurotoxic changes in addition to excess noise encountered in the work place. Thus, after identifying machinists who were employed in the mid- to late 1980's at LANL, we intended to analyze audiometric data available for these employees. Specifically we wanted to determine whether a pattern of chemically related hearing loss existed among machinists, pure noise-related hearing impairment should show a pattern of loss for higher frequencies first. Also, it was of interest whether there was an association between hearing loss and reported increases in liver enzymes and between hearing loss and certain job locations or solvent use. Furthermore, we intended to invite all former and current members of the machining department to take part in neuropsychological testing at LANL. All test results taken together, could have helped us to identify whether machinists at LANL have unusually high rates of cognitive abnormalities and whether the prevalence of these abnormalities are related to hearing loss pattern, liver function, and solvent use.

Yet, in order to test this hypothesis we needed to identify all members of the former machining department in which this cluster occurred. Unfortunately, this task was less than straightforward. A major problem was that work locations for LANL employees were not available in any routine records system maintained by LANL. Location codes on personnel records are used for administrative purposes and do not represent the work place in most cases. Furthermore, job titles are often non-descriptive of the actual work performed by the individual; i.e., a machinist might be called a technical staff member in the personnel files. The computerized files of the LANL epidemiologic group -- containing adequate job title information and radiation exposure data -- were not updated after 1977 due to funding constraints. In the absence of a better alternative, we queried this database and were able to identify about 1000 machinists according to job titles recorded at first or last employment at LANL. Out of these machinists, however, only 59 were found to be still actively employed at LANL (mean length of employment 24.8 years).

The current personnel filing system contains computerized records starting in 1991 and identified only machinists active in 1991 and still active as of the time of our query (1996). This record system identified 184 additional machinists, who had been first employed after 1979. Of these, 118 were still actively employed as of 1997 (mean employment duration of 14.1 years). Specifically, we don't know how many machinists we missed due to the gaps in the personnel data system at LANL. We encountered large gaps for the period 1978-1990 and potential further for 1991-1997, which could only be filled if it was possible to find and computerizing archived paper records. Yet, our efforts to retrieve archived data have proven very frustrating and inefficient. Someone would have to look through hardcopy, scanned, and/or microfiched records and/or a computer consultant would be required to bring some old electronic data on-line and do searches to find this information, this effort was outside the scope of our budget

Trying to restrict ourselves to the data collected until 1977, we evaluated the potential for contacting former employees by checking the local phone book for matching names. We were able to find matching individuals for about 12% of the 80 names checked. Again, to validly assemble a cohort or nested case-control group of current and mostly former machinists we would need to use an expensive state or national tracing system not feasible within the funding limits of this project.

Significant Findings: Pilot Study of Machinists

We have to conclude that an epidemiologic evaluation of medical surveillance at LANL is impossible without an extensive and expensive record retrieval and abstraction effort. Any study of work-related factors associated with chronic disease outcomes will encounter this problem. From this pilot project we concluded that currently it is impossible to identify groups of workers exposed to chemical agents in a systematic way from routine records kept at the LANL.

Usefulness of Findings: Pilot Study of Machinists

If these databases were maintained in a manner that would allow to link outcome data for workers to exposure measurements, they would be of great use for future worker health studies.

Cancer mortality from chemicals and radiation in Fernald uranium workers

Two data sets provided by the Comprehensive Epidemiology Data Resource (CEDR) referring to the same uranium processing workers employed at the Fernald facility allowed us to evaluate the contribution of chemical mixtures and radiation exposures to cancer mortality in a nuclear worker cohort. Dr. Jerome Wilson, the occupational physician responsible for this work force in the end 1970 and 1980s, conducted a study of respiratory morbidity at the Fernald facility for which he collected information on a number of chemicals such as solvents, kerosene, and cutting fluids used between 1950 and 1983. Facility industrial hygienists rated each job title and location and created a two or three category score for level of exposure to each of the chemicals in use. In addition, the length and timing of employment in a job and location has been recorded and was used to create duration measures of exposure and lag exposure. We combined this extensive chemical data set with the mortality files and the radiation data provided in CEDR and investigated whether and to what extent the different and multiple chemical exposures contributed to the mortality experience of Fernald workers. The results of these analyses have been documented in two recent publications attached to this report (Ritz 1999 a and b). (Appendix C)

Significant Findings:

Results indicated that Fernald workers exposed to ionizing radiation experienced an increase in mortality from total cancer (per 100 mSv external dose rate ratio (RR) = 1.92; 95% confidence interval (CI) 1.11, 3.32), radiosensitive solid cancer (RR = 2.00; 95% CI 1.02, 3.94), and lung cancer (RR=2.77; 95% CI 1.29, 5.95). Effects were strongest when exposure had occurred at older ages (>40 years). In addition, we observed an increase in lung-cancer mortality for workers exposed to >200 mSv of internal (alpha-) radiation (RR=1.92; 95% CI 0.53, 6.96).

Our results furthermore suggest that workers who were exposed to TCE experienced an increase in mortality from cancers of the liver. Cutting fluid exposure was found to be strongly associated with laryngeal cancers and, furthermore, with brain, hemato- and *lymphopoietic system, and bladder and kidney cancer mortality. Finally, kerosene exposure increased the rate of death from several digestive tract cancers (esophageal, stomach, pancreatic, colon and rectum cancers) and from prostate cancer. Effect estimates for these cancers increased with duration and level of exposure and were stronger when exposure was lagged.*

Usefulness of Findings:
Our results demonstrate the importance of a long follow-up time when studying solid cancers, the potential for bias due to worker selection associated with concomitant chemical exposures, problems of exposure measurement, confounding, and effect modification due to age at exposure and the limits of pooled analysis of uranium-processing workers that can only partially address these issues.

Evaluation of the Hearing Conservation Program at LANL

Introduction

Noise-induced occupational hearing loss continues to be one of the most frequent work-related diseases [1,2] and a clear link exists between noise exposure and hearing loss. [1,3,4] Occupational noise-induced hearing loss is a slowly developing sensorineural loss of hearing over a long period of time, usually ten or more years, as the result of exposure to continuous or intermittent loud noise. [5] It is almost always bilateral and the earliest damage occurs at the range of 3-6 kHz. This injury is irreversible and cannot be medically repaired. Hearing loss maybe exacerbated by synergistic effects of other exposures, such as vibrations or organic solvents. [3,5] In order to protect employees from this potential hazard, OSHA requires that employers shall administer a continuing, effective Hearing Conservation Program (HCP) whenever worker noise exposure exceeds the 8-hour time weighted average sound level of 85 dB measured on the A scale, or, equivalently, a dose of fifty percent. [6]

The goal of our project was to assess the effectiveness of the Hearing Conservation Program (HPC) implemented by the Los Alamos National Laboratories (LANL) and examine whether data stored at the facility would allow us to examine the contributions of noise and organic solvent exposure to hearing loss. A large quantity of audiometric data has accumulated in the LANL archives, but the potential risk of occupational noise or solvent induced hearing loss in the LANL worker population has never been systematically assessed nor has the effectiveness of the hearing loss prevention strategies implemented throughout the last decades ever been formally evaluated. The purpose of our research was to provide such an evaluation relying on data available at the facility in computerized and/or archived format. We received access to three databases: 1) noise sampling data; 2) hearing conservation data, and 3) audiometric testing data. A description of the complete LANL Hearing Conservation Program and the content of each of these databases can be found in Appendix 1 of this report.

We combined these data bases and examined (1) whether and to what extent it is possible to link case and non-case records to work locations and actual noise measurement performed by ESH-5 (Environmental Health and Safety) and (2) whether and which work-related risk factors for hearing loss can be examined epidemiologically after linking information from medical and industrial hygiene records.

Description of the LANL Hearing Conservation Program

The Hearing Conservation Program (HCP) has been designed to protect employees against hearing loss. LANL utilizes Air Force Regulation (AFR) 161-35 as recommended by DOE-Albuquerque [7]. Industrial Hygiene and Medical departments developed the LANL- HCP based on AFR 161-35 and Occupational Safety and Health Act (OSHA) 29 CFR 1910.95, Occupational Noise Exposure. Impact/impulse noise is being controlled based upon the threshold limit values of the American Conference of Governmental Industrial Hygienists.

The HCP applies to all LANL employees who are exposed to noise levels at or above fifty percent of the Occupational Exposure Limit (OEL), that is at 85 dB or more of A-weighted sound pressure level for eight hours in any 24-hour period or an equivalent exposure at higher levels for shorter times according to AFR 161-35. Employees, supervisors or health and safety personnel may request to enroll an employee in the HCP. Machine shop employees are automatically entered into the HCP regardless of the noise exposure. Supervisors, employees or health and safety personnel may request to remove an employee from the HCP. Usually, the reasons for removal are a change into a job without noise exposure or retirement. According to the LANL-HCP description, an employee is removed from the HCP whenever noise exposures above the action level no longer occur (action level is an 8-hour time weighted average of 80 dBA or a noise dose of 50% of the permissible OEL).

The purpose of the Hearing Conservation Program is to identify and characterize high noise areas, conduct measurements, and implement controls to reduce employee exposures to workplace noise. The HCP components include:

- A monitoring program designed to identify potentially high noise levels in the workplace
- Identification and notification of employees routinely exposed to hazardous noise
- Recommendation of engineering controls to reduce workplace noise and hearing protection for employees in potentially high noise areas
- Employee training (initial and annual)
- Audiometric testing and physician review
- Evaluation, investigation and reporting of suspected noise-induced hearing loss

LANL HCP includes all components recommended by NIOSH, except one. There is no program effectiveness evaluation component included in the LANL HCP.

Noise monitoring program

Description

Noise exposure monitoring is conducted via three noise surveys.

1. Walk around survey. A general survey is conducted to determine the locations and boundaries of hazardous noise areas. It is usually done with a Type 2 sound level meter and the results are used to plan a work shift sampling strategy.

2. Noise control survey. In this survey, Type 1 sound level meters are used with an octave band analyzer to obtain data that might to aid in selecting noise control methods.
3. Work shift sampling. This survey utilizes sample employees representative of each area in which over-exposure to noise may occur. Personal dosimeters are used to assess individual noise exposure.

Walk around and noise control surveys are considered area measurements and work shift sampling procedures are considered personal dosimetry measurements.

According to LANL HCP description, the records of noise measurement are being kept for a period consistent with DOE Order 1324.2A and will include as a minimum:

- Number, type and location of noise sources
- Number and identification of personnel in the work area and their daily exposure and duration (dosimetry is preferred)
- Type, model, ESH-5 number of test equipment and calibration data
- Location, date and time of noise measurement
- Noise levels measured and hazard radius
- Name of the person who made the survey

Concerns for HCP evaluation
We found that record keeping over the last decades was inconsistent leading to missing information. Approximately 75% of all records in the noise-sampling database (see description below) are missing actual noise measurement at each of the frequencies (0.125-8kHz). Sixty six percent of records are missing a verbal description of the exposure. HCP worker population is heterogeneous with regards to noise exposure, with some workers being exposed only to continuos noise, others to intermittent or impulse. Reportedly, some shop workers have "gray area" exposure, and may not qualify for enrollment into the HCP, yet may be exposed to occasional noise exceeding OEL. In addition, frequently workers are added to the HCP by the request of line management before the area can be evaluated. For example, a group might decide they need a small local carpentry shop. They organize the shop and then indicate which people are going to use the shop and request these employees to be put into the HCP. Thus, workers are placed and taken out of HCP continuously, sometimes without proper exposure identification.

Engineering controls and personal hearing protection

Description
Engineering controls are the first step at LANL in controlling excess noise exposure. These include isolating high noise machinery into separate rooms with audio isolation. If a particular location experiences noise level of 90dBA or above, a noise hazard warning sign is posted at the entrance. Administrative controls include worker shift rotations.

Hearing protection must be provided by line management for workers exposed to noise levels at or above action level. Hearing protection must be worn by employees exposed to noise levels at or above OEL. Employees may select their hearing protection devices from among several types which provide adequate protection.

Concerns for HCP evaluation

Records of hearing protection use do not exist. Employees store hearing protection devices at their work sites and apparently there is no uniform control to ensure compliance with the hearing protection requirements. Moreover, 99.8% of records in the audiometry database (see description below) are missing hearing protection information.

Employee training

Description

Initial and annual training is required for all employees exposed to noise at or above action level. The training program includes information on:

- The effects of noise on hearing
- The purpose and use of hearing protection devices, the advantages and disadvantages of each
- Instructions in the selection, fitting, use and care of hearing protection
- The purpose of audiometric testing and an explanation of the test procedures

The training class lasts for about an hour plus time for questions and a self-assessment test. A LANL group developed a test that can be sent to employees every other year. The test is a booklet including all of the above training and a self-test to send in after completion. The worker will need to receive an 80% or better score to pass. If the worker does not pass, he must attend the training class.

Concerns for HCP evaluation

No data exists about compliance with this HCP component.

Audiometric testing

Description

Audiometric testing has been performed at LANL since 1978. The recruitment of workers for testing prior to 1986, however, was not clearly defined. In 1986, a hearing conservation program has been adopted enrolling workers in a routine audiometric testing program at entry into a work area of high noise exposure (>85 decibel per 8 hr average). An employee is being assigned to the hearing conservation program by their supervisor when the work area is determined to fall under the criteria for high noise (established and monitored by ESH-5).

The audiometric testing program is performed and administered by ESH-2, the Medical program. ESH-5, Industrial Hygiene, identifies personnel who are exposed to noise at or above the action level and provides this information to ESH-2. Test results are maintained in the worker's medical record. Reportedly, no medical records are destroyed, even after termination of employment. Baseline audiograms must be performed within 6 months of an employee's first exposure and annual re-testing is required.

If an annual audiometry shows a threshold shift of 10 dB at any frequency compared to the baseline audiometry, a re-test is ordered after 48 hours of quiet. If a threshold shift still persists after the quiet period, a confirmation test is scheduled in 30 days. If the problem is not resolved the worker is referred to an audiologist and on-site further action is taken to investigate whether the hearing loss may be occupational noise-induced.

Audiometry is done using two MAICO 800 Automatic Computer Audiometers, which are being calibrated every day. Both machines are serviced every year by a special technician.

Concerns for HCP evaluation

Audiometric testing is performed on all LANL workers, including contractors (construction, guards) and county firefighters. It is not possible to differentiate between these workers given the information in the audiometry database. Furthermore, contract workers often are hired repeatedly for numerous separate projects by LANL. They are required to have audiometric testing at the day of hire; thus, multiple audiometric tests for the same person might be obtained within short periods of time. However, contract workers are not annually re-tested or systematically followed-up.

Audiometric testing is performed throughout the day. This may lead to underestimation of hearing loss if a baseline test was administered at the end of the day or to an overestimation of hearing loss if the baseline was administered in the morning, but subsequent testing was done at a different time. Also, workers ordered for a re-test after a 48-hour quiet period may forget about this requirement. Finally, there might be major problems with the accuracy of any audiometric reading because employees may not understand instructions, fail to respond properly, or are unable to concentrate during the test.

Program evaluation

Current HCP description does not include a program evaluation component. Reportedly, several audits have been conducted 1986-1991, one possibly by DOE-Albuquerque; however, we do not have any information pertaining to that. In addition, currently LANL HCP is being revised to use the ACGIH standards regarding hazardous noise exposure.

Specific Findings: Evaluation of HCP effectiveness

Our objective was to use epidemiologic tools to assess the effectiveness of LANL-HCP by observing changes in hearing threshold levels ('Standard Threshold Shifts' (STS)) dependent on membership in the HCP- program and documented noise exposure levels. In order to achieve this, we had to link audiometric test results with noise exposure data collected for individual workers and in area samples. Since our endpoints of interest were hearing level changes, only those workers with at least two audiometric tests reported in the audiometry database could be included in our evaluation effort. We did not employ any restrictions based on age or prior hearing loss. The first available audiogram was selected to provide a baseline value for hearing capacity and all subsequent audiograms were compared to the first one, thus, all threshold shifts presented in this report refer to differences between the first and last available audiogram.

Audiometry data exists for 19,875 workers, but only for 12,130 workers at least two tests are available. The noise-sampling database contains 5,481 records of noise sampling, 295 are noise measures for individual workers the rest area measurements; and the hearing conservation data refers to 676 individual workers. Thus noise-sampling database provided us with exposure data, but the majority of samples were area noise measurements and only a small number (about 5%) were personal measures. We found that most area noise measurements had been performed in Technical Area (TA) 3 which houses various shops including the machine shop and in TA 53. Unfortunately, we found that it was impossible to link measured workplace exposure levels to individual workers because the audiometric database does not contain worker location information, and no database exists or was made available to us that contains worker location and, thus, would allow us to match existing area noise measurements to individual workers. In fact, we were able to match only 155 individuals across all three available databases, and for no more than 106 of these workers personal noise measurements were available. This small group will be the basis for our analyses and we will refer to this group in the following as 'workers with noise measurements' (WWNM).

In Tables 1-3 we show the proportion of workers at LANL who experienced hearing loss in at least one ear according to different definitions and for two groups, i.e. workers with both audiometric and noise level measures (WWNM) and workers for whom we have audiometric data only. The OSHA definition - defining a change in hearing threshold for an average of 10dB or more at 2,3,4 kHz in either ear relative to a baseline audiogram [6]- clearly provides the most sensitive definition. According to the OSHA criteria, about one third of all workers for whom we have noise measurements experienced a loss in at least one ear while such a threshold shift was less prevalent among all workers ever tested audiometrically, about a quarter of them exhibited a shift. The observed crude difference between these two groups of workers persisted independent of which hearing loss definition was employed. Thus, the comparison might suggest that workers for whom industrial hygienists at LANL measured noise were not only a more highly exposed group but also experienced subsequent hearing loss at a higher rate.

For our preliminary comparisons of noise exposed with non-exposed workers we chose the OSHA standard threshold shift definition but relied on a threshold shift in both rather than either ear. We based this decision on our observation that audiometric data provided in the computerized database was not systematically corrected for measurement errors due to the failure of a worker to respond properly during audiometric testing. Thus, we believe that a shift in both ears can be considered a more reliable outcome. All comparisons presented are based on the difference between the first and last available audiometric test result. The follow-up period for audiometry among workers with noise measurements ranged from 0.6 to 20.6 years with a mean of 12.2 years. The earliest threshold shift increases for both ears were observed after a minimum 5-year difference between first and last audiometric test, but mostly shifts were observed after 15-20 years of follow-up and a minimum age of 40 years at the time of the last test. Thus, as expected, the proportion of workers who developed hearing loss increased as more time elapsed between the first and last available audiometry test result and as the population grew older.

Among the 106 noise monitored workers 52% had reportedly been exposed to noise levels of 85 dBA or more. Occupational hearing loss is expected to be bilateral and 24 workers (22.6%) in the WWNL group developed bilateral hearing loss (Table 5). Furthermore, 57 WWNL workers (53.8%) experienced hearing loss according to the OSHA criteria in at least one ear. Comparing the 106 exposed WWNL workers (>=85dBA) with those unexposed (<85dBA) we estimated a 2.8-fold increase in the risk for hearing loss (crude OR=2.81; 95% confidence limits 1.5, 7.5;

age-adjusted OR= 2.63; 95%CI 0.93, 7.43). As shown in Table 6, the risk of hearing loss steadily increased with an increase in dbA-level measured. Also, the risk increased by about 16% with every year that past between the first and last audiometric examination (table 6), that is after age-adjustment, we observed a two-fold increase for workers to experience a threshold shift with a 10 year interval and a 4-fold risk increase with a 15 and more year interval between the two audiometric examination. Finally, the largest effect, i.e., a 9-fold risk for hearing loss was experienced if the noise was recorded was being 'intermittent'. Most of the workers experiencing hearing losses due to intermittent noises worked in TA 40 or 3 and the noise was mostly due to the use of saws (see also Table 7).

Discussion

Our ability to evaluate LANL HCP effectiveness was limited mostly by a lack of worker location and job history data that would have allowed us to attribute noise level measurements for work areas to individual workers. Thus, our results are based on a quite small and possibly selective group of workers for whom individual noise measurements existed. Hearing loss is most likely work-related if an employee has a history of long-term exposure to noise levels sufficient to cause a pattern of hearing loss evident in audiometry tests. [3] Thus, for these 106 workers we had to assume that the noise levels measured and reported in the noise sampling database represented their actual exposure over an extended period of time. While it is critical to know the duration of noise exposure, we were only able to equate duration of exposure to the time elapsed between the first and the last available audiometry assuming that workers were consistently exposed at the levels reported at one time in the noise sampling database. It is obvious that this difference might not adequately reflect exposure duration. Nevertheless, we not only found a relation with increasing time between two audiometric tests but also with intensity (dbA) of exposure measured with personal monitoring devices.

There is no information on race or sex of individuals, however, reportedly, all employees are male. According to Environmental Safety and Health (ESH-5) management, a high percentage of workers are exposed to excessive noise outside of the workplace (e.g., recreational activities such as hunting and power tool use - chain saws), but information about such potential confounding factors was not available to us. Finally, workers might experience multiple exposures at their workplace, such as ototoxic solvents in addition to noise, but we were unable to obtain any chemical exposure data.

Conclusions

The major limitation of our evaluation of the LANL Hearing Conservation Program was our inability to link workers' audiometric data to area noise level measurements. Yet, for the small group of workers for whom noise measurements were available we saw a clear relationship with presumed duration of exposure, noise levels, and the noise type 'intermittent' mainly attributed to the use of saws in TA 40. We believe that the three databases provided to us could be of great use for further evaluation and help to implement appropriate prevention measures if these databases were maintained in a manner that would allow to link outcome data (audiometry data) for all workers to area noise measurements which represent 95% of all measurements taken at the facility.

In order to accomplish these goals in the future we thus recommend:

1. To create a noise distribution map for the facility and workplaces based on the noise monitoring program data collected by ESH-5 in order to identify technical areas (TA) with high rates of workers who experienced a STS.
2. To obtain historical lists of workers for each TA to allow a linkage of audiometry data with location and exposure data
3. To abstract archival database records to get a historic roster of employees enrolled in HCP.
4. Identify workers enrolled and not enrolled in HCP and compare the proportion of hearing loss experienced in each group given noise exposure levels and compare whether HCP effectiveness varied by technical area.
5. Conduct a match case-control study, i.e. match cases of hearing loss to non-cases enrolled in the audiometric monitoring program and matched according to year of baseline audiometric testing and age. For these cases and controls, compare the average noise levels encountered over the years at the facility and, in addition, retrieve information about protective equipment and exposure to solvents and metals to examine whether combined exposures increase the risk of developing hearing loss.
6. Evaluate the influence of bias due to the fact that exit exams are not mandatory and there might be a number of workers not reporting for these exams.

Usefulness of Findings: Evaluation of HCP effectiveness

Our results demonstrate that if routinely collected data were maintained at LANL in a manner that would allow to link outcome (audiometry) data for workers to area noise measurements, they would be of great use for future continued evaluations of the HCP and hearing loss prevention measures.

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Table 1. Frequency of 'standard threshold shift' (STS) for the **left ear** between the first and last available audiometry for workers with noise measurements (WWNM_group) and all workers with at least 2 audiometry measurements (audiometry group), by various standards (0 = no shift, 1 = shift present)

	WNL_group, 106 workers			Audiometry group, 12,130 workers		
	Shift	Frequency	Percent	Shift	Frequency	Percent
OSHA Average increase **10** dB at **2, 3, 4** kHz	 0 1	 72 34	 67.9 32.1	 0 1	 9186 2944	 75.7 24.3
NIOSH, current Increase of **15** dB at **.5, 1, 2, 3, 4, 6, 8, (10)**kHz	 0 1	 93 13	 87.7 12.3	 0 1	 11229 901	 92.6 7.4
NIOSH, 1972 Increase of **25** dB at **1, 2, 3,** kHz	 0 1	 103 3	 97.2 2.8	 0 1	 11937 193	 98.4 1.6
Mild hearing loss, consensus Increase of **40** dB at **1, 2, 3,** kHz	 0 1	 105 1	 99.1 0.9	 0 1	 12084 46	 99.6 0.4
Mild hearing loss, consensus Increase of **40** dB at **2, 3, 4** kHz	 0 1	 104 2	 98.1 1.9	 0 1	 12056 74	 99.4 0.6

Table 2. Frequency of 'standard threshold shift' (STS) for the **right ear** between the first and last available audiometry for workers with noise measurements (WWNM_group) and all workers with at least 2 audiometry measurements (audiometry group), by various standards (0 = no shift, 1 = shift present)

	WNL_group, 106 workers			Audiometry group, 12,130 workers		
	Shift	Frequency	Percent	Shift	Frequency	Percent
OSHA Average increase **10** dB at **2, 3, 4** kHz	 0 1	 59 47	 55.7 44.3	 0 1	 9044 3086	 74.6 25.4
NIOSH, current Increase of **15** dB at **.5, 1, 2, 3, 4, 6, 8,(10)** kHz	 0 1	 87 19	 82.1 17.9	 0 1	 11182 948	 92.2 7.8
NIOSH, 1972						

Increase of **25** dB at **1, 2, 3,** kHz	0 1	98 8	92.5 7.5	0 1	11933 197	98.4 1.6
Mild hearing loss, consensus Increase of **40** dB at **1, 2, 3,** kHz	 0 1	 105 1	 99.1 0.9	 0 1	 12068 62	 99.5 0.5
Mild hearing loss, consensus Increase of **40** dB at **2, 3, 4** kHz	 0 1	 103 3	 97.2 2.8	 0 1	 12046 84	 99.3 0.7

Table 3. Frequency of 'standard threshold shift' (STS) for **both ears** between the first and last available audiometry for workers with noise measurements (WWNM_group) and all workers with at least 2 audiometry measurements (audiometry group), by various standards (0 = no shift, 1 = shift present)

	WWNL_group, 106 workers			Audiometry group, 12,130 workers		
	Shift	Frequency	Percent	Shift	Frequency	Percent
OSHA Average increase **10** dB at **2, 3, 4** kHz	 0 1	 82 24	 77.4 22.6	 0 1	 10268 1862	 84.6 15.4
NIOSH, current Increase of **15** dB at **.5, 1, 2, 3, 4, 6, 8, (10)** kHz	 0 1	 96 10	 90.6 9.4	 0 1	 11663 467	 96.2 3.8
NIOSH, 1972 Increase of **25** dB at **1, 2, 3,** kHz	 0 1	 104 2	 98.1 1.9	 0 1	 12038 92	 99.2 0.8
Mild hearing loss, consensus Increase of **40** dB at **1, 2, 3,** kHz	 0 1	 106 0	 100.0 0.0	 0 1	 12101 29	 99.8 0.2
Mild hearing loss, consensus Increase of **40** dB at **2, 3, 4** kHz	 0 1	 105 1	 99.1 0.9	 0 1	 12095 35	 99.7 0.3

Table 4. Left, right, worst and both ears threshold shift of 10dB or more by exposure status (Exposure: 0 = unexposed, <85 dBA, 1 = exposed, 85+ dBA; Outcome: 0 = no shift, 1 = shift present)

Left ear

Exposed	Threshold shift 0	Threshold shift 1	Total
0	39	12	51
	76.47	23.53	
1	33	22	55
	60.00	40.00	
Total	72	34	106

Right ear

Exposed	Threshold shift 0	Threshold shift 1	Total
0	32	19	51
	62.75	37.25	
1	27	28	55
	49.09	50.91	
Total	59	47	106

Worst Ear

Exposed	Threshold shift 0	Threshold shift 1	Total
0	27	24	51
	52.94	47.06	
1	22	33	55
	40.00	60.00	
Total	49	57	106

Both ears

Exposed	Threshold shift 0	Threshold shift 1	Total
0	44	7	51
	86.27	13.73	
1	38	17	55
	69.09	30.91	
Total	82	24	106

Table 5. Left, right, and both ears threshold shift of 10dB or more by age group at the last available audiometry (0 = no shift, 1 = shift present)

LEFT EAR

Age group	Threshold shift 0	Threshold shift 1	Total
<30	4	1	5
	80.00	20.00	
30-39	20	3	23
	86.96	13.04	
40-49	27	12	39
	69.23	30.77	
50-59	15	12	27
	55.56	44.44	
60+	6	6	12
	50.00	50.00	
Total	72	34	106

RIGHT EAR

Age group	Threshold shift 0	Threshold shift 1	Total
<30	5	0	5
	100.00	0.00	
30-39	21	2	23
	91.30	8.70	
40-49	22	17	39
	56.41	43.59	
50-59	8	19	27
	29.63	70.37	
60+	3	9	12
	25.00	75.00	
Total	59	47	106

BOTH EARS

Age group	Threshold shift 0	Threshold shift 1	Total
<30	5	0	5
	100.00	0.00	
30-39	23	0	23
	100.00	0.00	
40-49	30	9	39
	76.92	23.08	
50-59	17	10	27
	62.96	37.04	
60+	7	5	12
	58.33	41.67	
Total	82	24	106

Table 6. Effect estimates for factors associated with a threshold shift of 10dB between first and last audiometric exam in both ears; results from logistic regression models (WWNM-group, N=106)

	Number of workers without STS	Number of workers with STS	Odds ratio (95% CI)
Age at last audiometric exam (in years)			1.11 (1.04, 1.19)
Years between the first and last audiometric exam (in years)			1.16 (1.01, 1.33)
dbA			
▪ <80	14	2	1.00
▪ 80-84	30	5	2.41 (0.32, 18.2)
▪ 85-89	28	8	2.87 (0.44, 18.8)
▪ ≥90	10	9	11.60 (1.54, 87.7)
Type of noise			
▪ steady	24	3	0.73 (0.16, 3.37)
▪ intermittent	4	7	9.03 (1.97, 41.3)
▪ impulse	3	1	1.67 (0.13, 21.4)
▪ mixed	5	3	2.78 (0.44, 17.6)

Table 7. Distribution of workers (WWNM-group, N=106) with and without a threshold shift of 10dB in both ears between first and last audiometric exam by technical area (TA)

Technical Area	Number of workers without STS	Number of workers with STS
unknown	0	1
3	35	7
9	2	0
16	4	0
35	7	1
39	1	0
40	6	7
41	1	1
43	2	0
46	4	0
50	1	0
53	13	5
55	5	0
59	1	2

Appendix 1
DATA SOURCES AVAILABLE FOR HCP EVALUATION

In all databases, workers are identified by their LANL identification number, a Z#.

Description

1. Noise sampling database.

Reportedly, this database contains information on LANL workers regardless of HCP enrollment status. Data records started in 1960, with regular measurements starting in 1970. This database includes noise exposure measurements, both personal dosimetry and area; location of measurement (Technical Area (TA), building and room number); description of exposure; date of sampling; duration of sampling; work group.
We have 5481 records in the noise sampling database, corresponding to 295 individual Z#.

2. Hearing conservation database.

Reportedly, this database contains information on people enrolled in the HCP. The records start in 1985. Database includes location (TA and building); LANL organization; nature of exposure; measurement date; noise level; date a person was added to the database; date deleted from the database; training date; deletion reason; HCP enrollment status (ever vs. never).
We have 1380 records in the noise database, corresponding to 676 individual Z#.

3. Audiometry database.

This database contains audiometry data on all workers at LANL, regardless of HCP enrollment status and including contractor employees (JCI - construction, PTLA - guards, and county firefighters). Regular records start in 1963. Database includes date of audiometric exam; audiometric measurements for left and right ear at 0.5, 1, 2, 3, 4, 6, 8, 10 kHz; interval until recheck; ear damage (e.g., tympanic membrane rupture); threshold shift.
We have 61054 records in the audiometry database, corresponding to 19875 individual Z#.

4. Birth year file.

This file just contains worker identification number and year of birth.
We have 30062 records in the birth year file, corresponding to 29917 individual Z#.

Concerns for HCP evaluation

The audiometry database does not contain information on worker location and start of employment. It appears that it is not possible to establish duration of noise exposure for each worker other than by looking at the time elapsed between the first and the last recorded audiometry. There is no single source of work history or worker location information contained in any of the databases. None of the available databases provides HCP enrollment status.

5. To develop and implement a risk-based framework and methodology that permits estimation of the incidence of adverse health impact predicted from environmental/biological exposure and enables development of surveillance programs and intervention strategies to prevent adverse consequences of exposure.

6. Assessing Risks from Exposures to Multiple Physical and Chemical Agents

Exposure to ionizing radiation in combination with chemicals is an important problem in many developed countries and is likely to be an issue in developing countries. Not only a growing concern at many hazardous waste sites, where various radioactive and toxic chemical wastes are buried, aggregate exposures to these two classes of hazardous agents are also common in the military, in the defense nuclear industry, and in many research laboratories. Moreover, in both the medical research and medical service sectors of modern economies, mixed exposure to ionizing radiation and certain chemicals can frequently occur. Mixed exposure to ionizing radiation and chemicals is also expected to be an important issue for many of the emerging research and technology industries in developed countries.

Very little quantitative analysis is currently available on the cumulative effects of exposure to multiple hazardous agents that have either similar or different mechanisms of action. Over the past several years, efforts have been made to develop the methodologies for risk assessment of chemical mixtures, but mixed exposures to two or more dissimilar agents such as radiation and one or more chemical agents have not yet been addressed in any substantive way. To address this issue, we carried out a review and evaluation of the current understanding of the health risks arising from mixed exposures to ionizing radiation and specific chemicals. We compiled information on how radiation/chemical exposures, when evaluated in aggregation, were linked to chronic health endpoints such as cancer and intermediate health outcomes such as chromosomal aberrations. We also consider the extent to which the current practices are consistent with the scientific understanding of the health risks associated with mixed-agent exposures. From this we identified research needs for assessing the cumulative health risks from aggregate exposures to ionizing radiation and chemicals. Our evaluation indicates that essentially no guidance has been provided for conducting risk assessment for two agents with different mechanisms of action (i.e., energy deposition from ionizing radiation versus DNA interactions with chemicals) but similar biological endpoints (i.e., chromosomal aberrations, mutations, and cancer). Our analysis reveals the problems caused by the absence of both the basic science and an appropriate evaluation framework for the combined effects of mixed-agent exposures. This makes it difficult to determine whether there is truly no interaction or somehow the interaction is masked by the scale of effect observation or inappropriate dose-response assumptions.

This effort resulted in a proposed framework for measuring and evaluating radiation/chemical exposures. This framework was applied to workers at the U.S. Department of Energy Savannah River Site in South Carolina where exposures to both benzene and ionizing radiation have been measured. The key findings and recommendations from this study are the following:

1) The environmental health sciences community needs an evaluation framework that makes possible consideration potential interactions between chemical agents and ionizing radiation.
2) The limited power of epidemiological studies may be inadequate to uncover the potential synergisms that would be important from a policy perspective.
3) Carefully designed studies of chromosomal aberrations may have the potential to reveal the synergisms caused by mixed exposure to genetoxic agents.

4) The environmental health community needs standardized procedures for characterizing the risks of mixed-agent exposures.
5) Uncertainties in extrapolation from experimental data to human risks must be properly characterized.
6) Risk assessment guidance must be explicit on procedures to address the combined effects of mixed-agent exposures.
7) There is an absence of case studies on the health effects of mixed-agent exposures.

Waste Incinerators as Case Study of Failure to Address Worker Exposure
Waste incineration has emerged over the last century as a viable strategy for (a) reducing the volume of municipal waste, (b) for reducing substantially the volume of chemical and biological hazardous wastes, (c) for destroying medically contaminated hospital waste, and (d) for producing energy. Whether waste incineration poses a health risk to occupational and residential populations has been the subject of continuous scientific debate. In November 1999, the National Research Council released a report titled "Waste Incineration and Public Health" that addressed pollutant emissions, exposures and health risks from waste incineration. We carried out a study to provide some background both on the health issues that have emerged for waste incineration and to discuss some of the issues raised in the NRC report. This work was published in the journal *Environmental Science and Technology*. In this report, we identified three areas in which the limitations and uncertainty in the data impact health effects assessments. First, there is very little emissions data for any event other that normal operation. Second, we still lack data needed to characterize intermedia transfers of emitted chemicals from ambient air to food webs and to indoor environments. Third, we note that the existing framework used to assess human exposures and health effects from incinerators has focused on local populations but excluded both workers and the larger regional populations.

Workers at incinerators are and understudied and important population for exposures to multiple chemical agents. Workers come into close contact with not only the stack emissions, but also with toxic pollutants captured in the air pollution control equipment, including electrostatic precipitators and bag houses. These must be cleaned out periodically, and high concentrations of dioxin and various metals have been measured in the air during these operations. Both personal and area sampling of workers cleaning out electrostatic precipitators at municipal incinerators demonstrated exposures greatly in excess of recommended limits for dioxins and metals (arsenic, lead, cadmium and aluminum). Elevated levels of dioxin and lead have been reported in the blood of municipal incineration workers. Higher concentrations of hydroxypyrene in the urine of municipal incineration workers indicate exposure to higher levels of polycyclic aromatic hydrocarbons; similarly, higher levels of urinary mutagens have been reported among refuse incinerator workers.

Research Products
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