Central and Eastern European Cohort Feasibility Study

Paolo Boffetta

Cancer risk from diesel engine emission in Central and Eastern Europe

Paolo Boffetta, International Agency for Research on Cancer; John Cherrie, Institute of Occupational Medicine, Edinburgh, UK

The project has the objective to assess the feasibility to conduct a multicentric historical cohort study of workers exposed to diesel engine emissions in Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Russia, Slovakia, and Slovenia. It will consist of the following tasks:

1. Development of a company questionnaire, aimed to collect standardized information on the size of the groups of workers that might be included in the cohort study and on their exposures.
2. Contact with companies potentially participating in the study. In each country, a collaborating centre has been selected. The feasibility study will focus on drivers, material-handling equipment operators and mechanics employed in major companies dealing with in land transport by road, construction and manufacture of transport equipment. In addition, non-metal miners will be considered.
3. Completion of the questionnaires. Questionnaires will be completed by the contact persons in each company and checked by the national collaborator. Limited exposure data will be collected on that occasion.
4. Assessment of the feasibility. Data from company questionnaires will be combined to estimate the size of the expected cohort in terms of exposure to diesel engine emissions and other relevant agents. A strategy for retrospective assessment of exposures will be devised. The assessment of the feasibility will be based on the expected study size, the likely extent of misclassification of exposure, the availability of an unexposed cohort, the possibility to look at subgroups of the overall cohort (e.g., women) and the quality of the available information on exposure to diesel engine emissions and other agents.
5. Development of the protocol for the full scale multicentric study.

The project will last 12 months. The list of collaborators is shown in the following table.

Country	*Collaborator*	*City*
Czech Republic	Z. Smerhovsky	Prague
	V. Janout	Olomouc
Estonia	M. Rahu	Tallinn
Hungary	P. Rudnai	Budapest
Latvia	M. Eglite	Riga
Lithuania	R. Raskeviciene	Kaunas
Poland	N. Szeszenia-Dabrowska	Lodz
Russia	M. Bulbulyan	Moscow
Slovakia	E. Fabianova	Banska Bystrica
Slovenia	M. Dodic-Fikfak	Ljubljana

Cancer and Diesel Exhaust Exposure in Railroad Workers: A Feasibility Study

Murray M. Finkelstein PhD, MDCM, Dave K. Verma PhD, CIH, ROH

GOAL OF FEASIBILITY STUDY

To determine whether a historical cohort study of lung cancer risk in relation to dose of diesel exhaust as measured by the elemental carbon method is feasible.

STUDY PARTNERS

- McMaster University Program in Occupational Health & Environmental Medicine
- McMaster University Occupational & Environmental Health Laboratory
- Canadian Pacific Railways
- Canadian National Railways

STUDY OUTCOMES

- Cohort Composition and Demographics
- Availability of Smoking Information
- Job Dictionary, Job Classifications
- Estimation of Numbers of Exposed Workers
- Identification of Information about Historic Exposures
- Current Sampling
- Historical Exposure Reconstruction

COHORT COMPOSITION AND DEMOGRAPHICS

- Collect copies of electronic employee databases.
  - estimate number of current, retired & separated employees
  - determine distributions of age, hire date, termination date, length of service
  - estimate numbers of deceased employees
  - approximately 100,000 workers

SMOKING INFORMATION

- Major confounder in the assessment of occupational lung cancer.
- Determine what smoking data are available

JOB DICTIONARY, AND JOB CLASSIFICATIONS

- Collect job dictionary
- Acquire job histories for individuals to determine distributions of exposures
- Interview long-term employees to evaluate historic work practices

ESTIMATION OF NUMBERS OF EXPOSED EMPLOYEES

Combine information from work records with information on exposure categories to estimate numbers of exposed workers in each category

IDENTIFICATION OF INFORMATION ABOUT EXPOSURES

- Determine availability of previous industrial hygiene assessments
- Collect copies of data
- Assess other information for usefulness in exposure reconstruction
  - (i.e. equipment purchases, shop layout, old work practices, ventilation records, etc.)
- Identify exposure to other toxic substances relevant to cancer

SAMPLING PROGRAM

- Identify current exposure levels and assess variability across job classifications
- Carry out side-by-side sampling program to explore the feasibility of converting data from older methodologies to the results of the elemental carbon method

HISTORIC EXPOSURE RECONSTRUCTION

- Obtain old locomotives and simulate historic ventilation and work practices
- Collect samples of current conditions in summer and winter
- What were the highest exposed occupations

Railroad shop area sampling set-up

Personal sampling set-up

Locomotive area sampling set- up

PRELIMINARY INVESTIGATIONS

A Comparison of Sampling &Analytical Methods for Assessing Occupational Exposure to Diesel Exhaust in a Railroad Work Environment

Dave K. Verma, Lorraine Shaw, Jim Julian, Kathy Smolynec Chris Wood and Don Shaw

Abstract

Methods of assessing occupational exposure to diesel exhaust were evaluated in a railroad work environment. The American Conference of Governmental Industrial Hygienists (ACGIH)-recommended elemental carbon and respiratory combustible dust methods of sampling and analysis for assessing diesel exhaust were included in the study. A total of 215 personal and areas samples were collected using both size-selective (nylon cyclone and Marple) non-size-selective samplers. The results demonstrate that the elemental carbon is suitable for the railroad work environment while respirable combustible dust method is not. All elemental carbon concentrations measured were below the formerly proposed ACGIH Threshold Limited Value of 0.15 mg/m3. The concentrations of oxides of nitrogen (nitric oxide and nitrogen dioxide) were also found to be below their respective threshold limit values. Comparison of elemental carbon and respirable dust measurements showed consistent relationships for most sampling locations with respirable combustible dust concentrations 12 to 53 times higher than the elemental carbon levels.

** Accepted for publication in the Applied Occupational and Environmental Hygiene Journal **

McMaster University HEALTH SCIENCES

This study is funded by a grant from the Health Effects Institute

Canadian Railroad Workers Cohort Feasibility Study

Murray Finkelstein

U.S. Truckers Cohort Feasibility Study

Eric Garshick

TITLE:

Lung Cancer Risk and the Quantitative Assessment of Diesel Exhaust Exposure in the U.S. Trucking Industry. E Garshick, TJ Smith, F Laden, E Larkin, D Dockery, FE Speizer. Brockton/West Roxbury VAMC and Channing Laboratory, Brigham and Women's Hospital; Harvard School of Public Health and Harvard Medical School, Boston, MA, USA.

ABSTRACT:

This project will evaluate the feasibility of conducting a retrospective cohort study of workers drawn from the U.S. trucking industry to quantify the relationship between lung cancer mortality and diesel exhaust exposure. An over-all objective is to identify a population of workers in the U.S. trucking industry exposed to diesel emissions so that a reasonably precise estimate of a small to moderate excess of lung cancer attributable to exposure can be detected. An exposure assessment strategy that will be developed that will provide quantitative dose estimates (cumulative exposure) for each subject based on his personal job history and an assessment of current exposure. We have contacted three large unionized trucking companies who have over 60,000 workers employed. These companies have agreed to provide personnel and truck purchase and maintenance records for review so that the feasibility of using these records to design an epidemiologic study can be assessed. Based on truck purchase and maintenance records for trucks at each terminal, the specific truck type that a worker used can be determined. We will then assess the feasibility of linking yearly Teamster job code to work at a specific terminal or office to develop a personal profile of truck use for each worker. The exposure assessment strategy will include a determination to assess if it is feasible (1) to collect suitable exposure measurements to develop a statistical model to assess current exposure; (2) to use the wide range of company and other records to reconstruct estimates of past exposures, using emission factors for the effects of changes in vehicles; (3) to assess the feasibility of assessing potential bias and precision of the exposure estimates. It will be also be determined if there is a range of significantly different exposures to markers of diesel exposure. These markers will include polycyclic aromatic hydrocarbons (PAH), nitro-PAH, and elemental carbon in particles less than 1 μm in diameter. These will be supplemented by direct reading measurements of particulate matter < 1 μm in diameter and measurements of air quality in truck cabs and indoor work sites (CO, CO_2, temperature, and relative humidity) to identify sources of exposure and short-term variations in exposure. The results of this feasibility study will allow us to design a retrospective cohort study that will have greater than an 80% power to detect a relative risk of lung cancer between 1.2 to 1.3 attributable to diesel exposure in trucking company workers.

Diesel Aerosol Exposure

David Kittelson

DIESEL AEROSOL EXPOSURE

D. B. Kittelson, W. F. Watts, Department of Mechanical Engineering
and G. Ramachandran, School of Public Health
University of Minnesota

ABSTRACT

By number count, most diesel aerosol is in the nuclei mode with a particle diameter < 50 nm, and a number median diameter between 15-20. However, most of the aerosol mass is in the accumulation mode (50-nm to1000 nm), with a mass median diameter between 100-200 nm. The proposed Threshold Limit Value for diesel particulate matter (DPM) <1.0 μm (50 $\mu g/m^3$), and EPA's emission and air quality regulations are also based on mass measurements. When available, mass concentrations of DPM exposure have been used in quantitative risk assessments. Less information is available on the physical and chemical composition of diesel aerosol collected under real-world conditions.

The objective of this project is to validate diesel aerosol measurement techniques and to provide a more comprehensive evaluation of DPM exposure. Aerosol instruments capable of determining the number, volume, surface area and mass size distributions and particle associated total polycyclic aromatic hydrocarbon content in near-real-time will be combined with time-weighted average, personal exposure measurements of elemental and organic carbon (EC, OC) to assess exposure. A limited number of size fractionated samples will be collected for chemical characterization.

Diesel aerosol sampling will focus on the University of Minnesota's transit system. Personal samples will be collected on bus commuters, parking garage attendants, and mechanics to obtain distributions of exposures for these similarly exposed groups. Area samples will be collected at bus stops, parking garages, and garage maintenance facilities. These sampling locations represent environments where both diesel and gasoline powered vehicles operate on a regular basis in various ratios. Comparison of these footprints will make it possible to apportion the sampled aerosol by source, either diesel or non-diesel, and allow the estimation of DPM concentration and exposure.

Ambient Sampling of Diesel Particulate Matter

William Pierson

AMBIENT SAMPLING OF DIESEL PARTICULATE MATTER

William R. Pierson, Alan W. Gertler, John C. Sagebiel, C. Fred Rogers, and John A. Gillies
Energy and Environmental Engineering Center
Desert Research Institute
Reno, NV

Thomas A. Cahill
University of California
Davis, CA

ABSTRACT

The Health Effects Institute plans to begin studies in the year 2000 to provide dose-response data on the relation between human cancer risk and long-term exposure to diesel emissions. In order to provide background information on the physical and chemical characteristics of diesel particulate matter, we will perform an on-road study of emissions in a tunnel to obtain the following:

1. Chemically speciated diesel profiles for use in source apportionment between diesel and other constituents in ambient-air experiments. This is necessary to quantify the diesel contribution to ambient particles.
2. Particle-number and chemically speciated size-segregated particle distributions to determine in the real world the distribution of diesel particles. Recent dynamometer experiments have reported a greater number of 0.0075-0.046 μm particles from current diesel engines than from older ones. This study would resolve the question of whether or not diesel vehicles emit large numbers of ultrafine particles and, more importantly, whether in the real world the small particles are conserved.
3. Determine by comparison with years past how much improvement there has actually been in diesel particulate mass. Because of roll-over (and possibly other factors) the improvement will be less than that seen in year-to-year dynamometer tests. This is important if HEI is to incorporate retrospective data in their future studies.
4. Particulate emission rates from light-duty gasoline vehicles. Recent studies have found light-duty vehicles may actually contribute more to the observed particle levels than emissions from diesels.

In order to accomplish these objectives, four tasks will be performed:

Task 1: Planning: Based on our previous experience with on-road measurements of vehicle emissions in the Tuscarora Tunnel, we will arrange with Pennsylvania Turnpike personnel for access to the tunnel. As part of this task, we will also develop the necessary experimental protocols and checkout and calibrate all equipment prior to shipment for installation at the tunnel.

Task 2: Field Operations: Travel to the site and install equipment at stations within the tunnel. Perform 20 experimental runs within the tunnel during a fourteen-day period (one day for setup, ten days for measurements, and one day for takedown.) The sampling setup will have an inlet and outlet station. Each station will consist of:

- Tedlar bag sampler for total THC, NO/NO_x, CO, and CO_2
- Tenax sampler for semi-volatile hydrocarbons (C_6 to C_{20})
- IMPROVE $PM_{2.5}$ sampler for inorganic particulates (mass, ions, metals, OC/EC, b_{abs}, and H^+)

- DRUM sampler for size segregated mass and metals measurements (0.07-0.24; 0.24-0.34; 0.34-0.56; 0.56-0.75; 0.75-1.15; 1.15-2.5; 2.5-5.0; and 5.0-10.0 μm aerodynamic diameter)
- TGIF/PUF/XAD sampler for PAHs
- Propeller anemometer for air flow measurements
- Canister sampler for SF_6

In addition, a scanning mobility analyzer will be located along the tunnel to obtain size-fractionated particle number counts. Sampling periods will be chosen to represent different fleet mixes. As part of the vehicle characterization aspect of the task, we will obtain traffic measurements including counts and vehicle type and vehicle speeds.

Task 3: Data Processing and Data Analysis: Data from the field measurements will be transferred to a common database, validated, and, employing already existing software, used to calculate on-road emission factors. Following laboratory analyses, size-segregated mass emission factors and organic and inorganic speciated emission factors will be calculated. Chemical profiles for use in apportioning the diesel contribution in ambient particulate matter will be prepared. These results will be compared with those from previous studies to assess the changes in diesel emissions since the early 1970s.

Task 4: Reporting: We will prepare at least one publication for peer-reviewed publication, progress reports for HEI, and a final report for HEI.

Exposure Measurements in Mines

Barbara Zielinska

DIESEL EMISSIONS EXPOSURE MEASUREMENTS IN UNDERGROUND MINES

Barbara Zielinska, Eric Fujita, Fred Rogers, Larry Sheetz, and John Sagebiel
Desert Research Institute, 2215 Raggio Parkway, Reno, NV 89512
and
Pierre Mousset-Jones and James Woodrow
University of Nevada, Reno, NV 89557

Abstract

The *overall objective* of this proposal is to develop a method to accurately quantify the exposure of underground miners to diesel particulate matter (DPM), respirable dust, and oil mist concentrations. The *specific aims* are: (1) to characterize chemical composition and particle size distributions of organic and inorganic contaminants from specific sources and in ambient air in underground gold mines; (2) to apportion the contribution of specific sources (e.g., diesel equipment, mechanical particle generation, oil mist, etc.) to the total ambient airborne contaminant load in the mines; (3) to determine exposures for mine workers from these sources. We propose to use Chemical Mass Balance modeling to provide estimates of DPM, oil mist concentrations and other contaminants in underground mines, including cigarette smoke. To establish specific chemical profiles, detailed chemical analyses will be performed for diesel exhaust, diesel fuel, drilling and lube oil, and other possible aerosol sources in mines, expanding the current database related to diesel exhaust and oil mist exposure. To apportion aerosol in mines to its respective sources, the mine atmosphere will be sampled using size-selective samplers. In addition, in response to questions raised recently regarding the health impacts of ultrafine particle emissions, we propose to characterize particle-size composition of diesel exhaust. Since individual workers are exposed to wide variations in contaminant concentrations as they perform different functions in different locations, we will supplement ambient air analysis with personnel monitoring. We postulate that it is possible to obtain similar chemical information with both medium-volume, fixed-site sampling and with low-volume portable, personal sampling, the latter to be used for personal exposure measurements. Potential exposures will be calculated for workers in different job classifications. The results obtained in this study will be applicable to other programs requiring methods to monitor and assess exposure to diesel emissions and provide information of exposure of unique populations to diesel particulate emissions.

SESSION VI

What Will Epidemiology Studies Now Underway Tell Us About Exposure-Response? *(continued)*

Charles Poole, Co-Chair

Gerald van Belle, Co-Chair

Michael Attfield

Debra Silverman

Daniel Yereb

Mustafa Dosemeci

Session VI focused on various aspects of a large epidemiologic study of U.S. non-metal miners. Presentations were given on the cohort, case-control, industrial hygiene, and historic exposure assessment methods of the study, which is being conducted by investigators at NCI and NIOSH.

U.S. Non-Metal Miners: Cohort Study

Michael Attfield

A COHORT MORTALITY STUDY OF LUNG CANCER AND DIESEL EXHAUST AMONG NON-METAL MINERS

Michael Attfield,[1] Patricia Schleiff,[1] Rebecca Stanevich,[1] Daniel Yereb,[1] Debra Silverman[2] Mustafa Dosemeci,[2] Jacqueline Prince,[2] and Nathaniel Rothman,[2]
1 National Institute for Occupational Safety and Health; 2 National Cancer Institute.

Although many studies have been undertaken to assess mortality associated with exposure to diesel exhaust, few studies have employed quantitative exposure measurements of diesel exhaust directly in their analyses. To fill this need, the National Institute for Occupational Safety and Health (NIOSH) and the National Cancer Institute (NCI) are conducting a retrospective cohort mortality study of non-metal miners to investigate risk of lung cancer mortality in relation to quantitative measures of exposure to diesel exhaust. In addition, it will determine whether there is evidence of elevated mortality from other causes among diesel exhaust exposed miners.

A feasibility study undertaken jointly by NCI and NIOSH between 1992 and 1994 gathered information on employment, personnel records, and underground diesel usage at non-metal mines. The non-metal mining industry was selected for study because of the potential for high levels of diesel exhaust exposure in the absence of confounding by exposure to radon and other possible lung carcinogens. Twenty-four mines that had used diesels before 1970 and which employed more than 59 workers were selected for potential inclusion in the study. These mines were ranked, based on examination of existing industrial hygiene data, historical data on worker exposures, samples of personnel records, and other information. Expected numbers of lung cancer cases were derived by applying national mortality rates to the samples of personnel records available for each mine. Summation of these expected numbers by suitability rank showed that the first 10 mines would provide enough cases for a study of sufficient power. These 10 mines included four potash mines, three trona (soda ash) mines, two salt mines, and one low-silica limestone mine. Extensive industrial hygiene surveys had been undertaken at seven of the 10 mines around 1975 - a time when many mines were experiencing their peak usage of diesels underground. A special industrial hygiene survey undertaken at one of the 10 mines indicated that diesel exhaust exposures in certain areas underground were 5 - 40 times higher than exposures reported to be experienced by railroad workers or truck drivers.

The purpose of the cohort study is to identify any causes of death (especially lung cancer) that are elevated in the cohort, and if so, relate the elevations to extent of diesel exhaust exposure. To achieve this goal, the study cohort includes all underground, and surface workers (excluding administrative workers) who were employed in the candidate mines for at least one year during the period between the date of dieselization of each mine and December 31, 1997. Most surface workers are essentially not occupationally exposed to diesel exhaust; thus the cohort study will include a wide range of exposure to diesel exhaust (about 50% unexposed, 25% low/moderately exposed, and 25% high exposed, with underground workers comprising most of those exposed.) The study cohort will be followed for vital status through December 31, 1997. Since the earliest date of dieselization of any of the proposed study mines was 1950, the follow-up period will range up to 48 years. Given the expected level and distribution of exposure, and based on a cohort of 8,200 miners with 1 or more years of exposure, the cohort study has greater than 90% power to detect a trend in lung cancer mortality of RRs from 1 to 1.4 to 2.0 for low/unexposed to moderate to high exposure, at a 5% two-sided alpha level.

Standard procedures are being employed to ascertain vital status, including: SSA mortality files, application of data from the National Death Index, IRS address information, Postmasters, and other sources. Analysis of the cohort study will be undertaken in two phases. Phase I will employ indirect

surrogates of diesel exposure in order to explore exposure-response. These will include work and tenure in jobs known *a priori* as having high, moderate, and low exposures (e.g., face, other underground, and surface work). It may also be possible to include preliminary data from the IH surveys and elsewhere in order to help inform and define the exposure categories. Causes of death will be divided into those of *a priori* interest and those of *a posteriori* interest. The former comprise: lung cancer, bladder cancer, kidney cancer, colon cancer, cancer of the rectum, multiple myeloma, lymphoid leukemia, Hodgkin's disease; cerebrovascular disease, arteriosclerosis, pneumonia, influenza, cirrhosis of the liver, emphysema, and chronic respiratory disease. Excesses of these causes have been found in one or more studies that have looked at mortality and exposure to diesel exhaust. *A posteriori* causes will be considered as hypothesis generating.

The Phase II analysis of this study will evaluate quantitative exposure-response using various exposure metrics, such as cumulative exposure, average exposure and maximum exposure. In addition, time-dependent aspects of exposure, including lagged estimates of exposure will be used to eliminate the effect of later exposures in examining the exposure-response relationship. In these analyses, the main surrogate of diesel exposure will be elemental carbon, derived directly from current measurements of exposure levels, and indirectly by conversion of historical surrogates, such a nitrogen dioxide, to elemental carbon levels by means of relationships derived from side-by-side sampling in the current IH surveys. Other primary surrogates will be submicrometer particulate, and submicrometer combustible dust.

Although the mines selected for study have been documented as having low levels of exposure to radon, silica, and arsenic, we have sampled for these substances and also for asbestos during the IH surveys to confirm that levels are below that which might be expected to cause confounding. If unforeseen elevations occur, and it appears that confounding could be a problem, control for these variables will be included in the analysis. Indirect adjustment for smoking will be made using the Axelson technique. For the mines that were in the 1976 MSHA/NIOSH study, there is smoking information available on the cross-section of workers who took part in the study. The nested case-control study, which will be using data from the cohort study, will permit more rigorous examination of smoking and other factors.

Data collection for the study began in February, 1998. Currently, IH studies have been completed for eight of the nine operating mines in the study. Reports on these surveys are being sent to each mine as they become available. Personnel record collection is virtually complete at six mines, and partially complete to various degrees at the remaining four mines. As of September, 1998, we had fully or partially entered records for about 11,800 individuals to our mortality database, consisting of demographic data, work history, next of kin, and any existing vital status data. Based on a preliminary tabulation of miners who worked 1 year or more before 1979, it appears that the intended study size of 8,200 miners will be achieved. Mortality vital status follow-up has commenced for two mines.

Statistical analysis will begin following completion of data entry and finalization of follow-up, and is expected to start towards the end of 2000. The Phase I report is scheduled for completion two years later, with possibly an interim presentation earlier. The final task of the cohort study will be to undertake the Phase II analysis, with a report planned for 2003.

A COHORT MORTALITY STUDY OF LUNG CANCER AND DIESEL EXHAUST AMONG NON-METAL MINERS

Michael Attfield

Patty Schleiff

NIOSH, Morgantown, WV

Researchers

NIOSH	NCI
Michael Attfield	Debra Silverman
Rebecca Stanevich	Mustafa Dosemeci
Patricia Schleiff	Nathaniel Rothman
Daniel Yereb	Jacqueline Prince

Study Genesis

- Increasing interest in health effects of diesel exhaust
- Need for more information on quantitative exposure-response

Feasibility Study Purpose

- Designed to assess whether sufficient data of suitable quality existed for application to a valid mortality study
- Collaborative project by NIOSH and NCI

Feasibility Study Evaluated -

- Extent of diesel usage (large range of exposures)
- Start of diesel usage (adequate latency period)
- Absence of confounding exposures
- Availability of past industrial hygiene data

Feasibility Study Evaluated -

- Extent of diesel usage (large range of exposures)
- Start of diesel usage (adequate latency period)
- Absence of confounding exposures
- Availability of past industrial hygiene data
- Mine size

Feasibility Study - Outcome

- Sufficient data of a suitably high quality were available to enable the completion of a valid mortality study
- In 1994 NCI and NIOSH began to develop the protocol for the main study

The overall study

- Cohort mortality study
- Nested case-control study of lung cancer
- Current exposure assessment
- Historical exposure reconstruction
- Biomarker component

The Cohort Mortality Study - Objectives

- To identify causes of death (especially lung cancer) which may be elevated in the cohort.
- To assess any elevations in certain specific causes of death in relation to extent of exposure to diesel exhaust.

The Cohort Mortality Study - Methods

A priori causes of death for study include:

- Lung cancer
- Bladder cancer, kidney cancer and other causes noted as having elevated death rates in previous studies.

The Cohort Mortality Study - Methods

The cohort includes:

- All employees, apart from pure administrative workers, who worked 1 year or more since date of dieselization at each mine

The Cohort Mortality Study - Methods

The analytical approach is as follows:

- A standard SMR person-years approach.
- Axelson adjustment for smoking.
- Model fitting using Cox and Poisson regression.

The Cohort Mortality Study - Methods

Exposure-response will be assessed using:

- Elemental carbon exposures.
- Other current surrogates - respirable combustible dust, submicrometer particulate.
- Historical surrogates, e.g. NO_2.
- Tenure and job.

The Cohort Mortality Study - Methods

Exposures will be developed from:

- Current industrial hygiene surveys.
- Historical measurements converted to elemental carbon levels using factors derived from current side-by-side sampling.
- Other pertinent data.

The Cohort Mortality Study - Mine Selection

The expected number of lung cancer cases for each mine was derived by:

- Entering the 10% sample of feasibility study work histories to a database.
- Using the OCMAP mortality program to derive expected numbers based on the person-years.
- Adjusting for other causes and extrapolating to the full mine employment.

The Cohort Mortality Study - Mine Selection

Mines were ranked by:

- Expected number of lung cancer cases.
- Record quality.
- Availability of past exposure data.
- Exposure level.
- Mine currently operating or not

The Cohort Mortality Study - Mine Selection

Ten mines were selected:

- 4 Potash mines
- 3 Trona (soda ash) mines
- 2 Salt (halite) mines
- 1 low-silica Limestone mine

- 4 back-up mines also selected

The Cohort Mortality Study - Mine Selection

The ten mines:

- provide excellent power for the cohort and case-control studies (see later)
- have low levels of potential confounders, (e.g., silica, radon, arsenic, asbestos)
- have extensive prior exposure data (seven mines) from research surveys by MESA in 1976 (now MSHA)

The Cohort Mortality Study - Mine Selection

The ten mines:

- provide excellent power for the cohort and case-control studies (see later)
- have low levels of potential confounders, (e.g., silica, radon, arsenic, asbestos)
- have extensive prior exposure data in seven cases
- have good personnel records

The Cohort Mortality Study - Mine Selection

The ten mines:

- Average year of dieselization was 1961 (1950 - 1967)
- 44% of employees work underground
- Six mines classified as high exposure, two as moderate, and two as low (relative to mining operations).

The Cohort Mortality Study - Mine Selection

Past IH data for each mine from 1976 - 78 includes:

- Between 600 - 940 samples in total
- About 200 personal samples
- About 100 area samples
- About 150 general air samples

(Above numbers refer to measurements, not locations.)

The Cohort Mortality Study - Study Power

On assumption that 50% of workers are high exposed, 25% have moderate, and 25% have low/zero exposure within the mines,

- the cohort study has 90% power to detect a trend in risk from 1 to 1.4 to 2.0 for low/zero, moderate, and high exposure, respectively, at a 5% alpha level

The Cohort Mortality Study - Progress Report

Industrial hygiene surveys:

- Surveys began in February 1998.
- Eight IH surveys have been completed.
- Each survey involved the collection of about 500 area measurements and 300 personal measurements over five days.
- Two mine reports are under review, with others to follow.

The Cohort Mortality Study - Progress Report

Record collection and data entry:

- Record collection began in February 1998.
- Record collection is virtually complete for four mines, and partially complete for five.
- Over 16,500 records are entered, with about 9,000 in hand.
- Estimated that 31% of all miners worked 1 or more years before 1979.

The Cohort Mortality Study - Progress Report

Mortality follow-up:

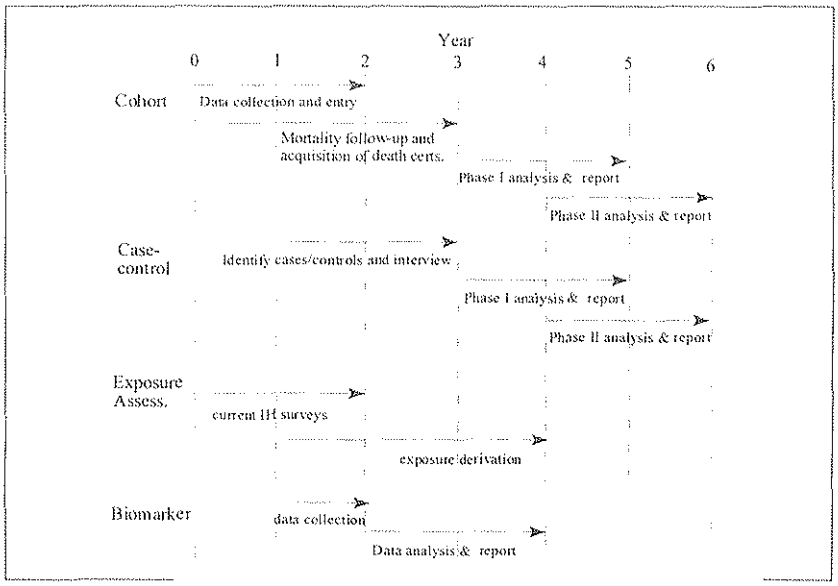
- Has begun for two mines.
- Additional mines will be started when record collection/verification/checking is complete for each.

The Cohort Mortality Study - Reporting

Results from the mortality analyses will be presented in two phases -

- Phase I - findings based on analysis by indirect surrogates, such as tenure and job.
- Phase II - findings based on analysis using quantitative exposure assessments.

The Cohort Mortality Study - Schedule



The Cohort Mortality Study - Schedule

- Complete data collection and data entry - end of 1999.
- Complete vital status follow-up - end of 2000.
- Complete Phase I analysis and report - end of 2003
- Complete Phase II analysis and report - end of 2004

U.S. Non-Metal Miners: Case-Control Study

Debra Silverman

A NESTED CASE-CONTROL STUDY OF LUNG CANCER AND DIESEL EXHAUST EXPOSURE IN A COHORT OF NON-METAL MINERS Debra T. Silverman, Mustafa Dosemeci, Nathaniel Rothman, Jacqueline Prince (National Cancer Institute); Michael Attfield, Rebecca Stanevich, Daniel Yereb, Patricia Schleiff (National Institute for Occupational Safety and Health)

The National Cancer Institute, in collaboration with the National Institute of Occupational Safety and Health, is conducting a case-control study of lung cancer and diesel exhaust exposure in a cohort of about 8,200 non-metal miners. The cohort includes all workers (except administative workers) who were employed for at least one year in a study mine from the date of dieselization of each mine through 1996. The main purpose of the nested case-control study is to evaluate the association between levels of diesel exposure and lung cancer mortality among non-metal miners, while controlling for cigarette smoking and other potential confounding factors.

The case series will include all deaths from lung cancer as specified on the death certificate that are identified during the follow-up stage of the cohort. Pathology slides of tumor tissue from all histologically confirmed cases of lung cancer will be obtained for review. The objective of the slide review is to confirm the death certificate diagnosis of lung cancer, as well as to determine the histologic subtype.

Four controls will be selected for each case by random sampling from among all members of the study base who were alive prior to the day the case died (i.e., incidence density sampling). Controls will be individually matched to the case on mine, gender, race/ethnicity, and year of birth (within five years). Exposure in controls will be truncated at the age that the case died.

A structured questionnaire will be developed to elicit information on the following factors: date of birth, date of death, race/ethnicity, gender, history of smoking, exposure to environmental tobacco smoke, dietary factors, lifetime employment history, and medical history. Smoking histories will be supplemented with relevant information from company medical records and smoking data collected during a 1976-1978 cross-sectional morbidity survey.

The questionnaire will be administered to next of kin of cases and deceased controls by telephone using interviewers trained for this purpose. Direct interviews will be conducted with living controls by telephone. Informed consent will be obtained from all respondents before the interview is conducted. Based on data from previous studies, we anticipate a 75% response rate for the next-of-kin interview. We expect to obtain smoking history data on an additional 10% of subjects when the interview data are supplemented with data from additional sources, yielding a total response rate of 85%.

Data from the case-control study will be used to estimate the risk of dying from lung cancer associated with several measures of occupational exposure to diesel exhaust (e.g., average intensity of exposure, duration of exposure, and cumulative exposure). Conditional logistic regression analysis will be used to quantify the exposure-response relationship between lung cancer and these measures of diesel exhaust exposure after adjustment for confounding factors. The role of cigarette smoking as a modifer of the effect of diesel exhaust exposure on lung cancer risk will be evaluated if numbers permit.

The cohort of about 8,200 subjects is expected to yield a minimum of about 160 lung cancer deaths based on the assumption of a trend in risk of lung cancer from 1 to 1.4 to 2.0 with increasing exposure to diesel exhaust. Based on a response rate of 85%, we expect to have a minimum of about 140 lung cancer cases and 560 controls, yielding a power of 80% to detect a trend in odds ratios of 2.0 for high exposure, 1.4 for low/moderate exposure, and 1.0 for no exposure, after adjustment for smoking ($\alpha = 0.05$).

A NESTED CASE-CONTROL STUDY OF LUNG CANCER AND DIESEL EXHAUST EXPOSURE

NCI

Debra Silverman
Mustafa Dosemeci
Nathaniel Rothman
Jacqueline Prince
Capri-Mara Fillmore

NIOSH

Michael Attfield
Rebecca Stanevich
Daniel Yereb
Patricia Schleiff

PURPOSE OF STUDY

To evaluate the association between levels of diesel exposure and lung cancer mortality among non-metal miners, while controlling for cigarette smoking and other potential confounding factors

CASE SERIES

- All deaths from lung cancer identified during the follow-up stage of the cohort
- ≥160 lung cancer deaths, assuming doubling of risk in the heavily exposed
- Pathology review

CONTROL SERIES

- Controls: Cases = 4:1
- Controls will be selected by random sampling from among all members of the study base who were alive prior to the day the case died
- Matching factors: Mine
  Gender
  Race/Ethnicity
  Year of Birth
- Exposure in controls will be truncated at the age that the case died

INTERVIEWS

- Telephone interviews
- Next of kin: Dead Subjects
  (All cases and dead controls)
- Direct interviews: Living controls

DATA ANALYSIS

- Conditional logistic regression to quantify exposure-response relationship between lung cancer and diesel exhaust exposure, after adjustment for confounding factors
- Measures of exposure:
  - Average intensity
  - Duration
  - Cumulative exposure

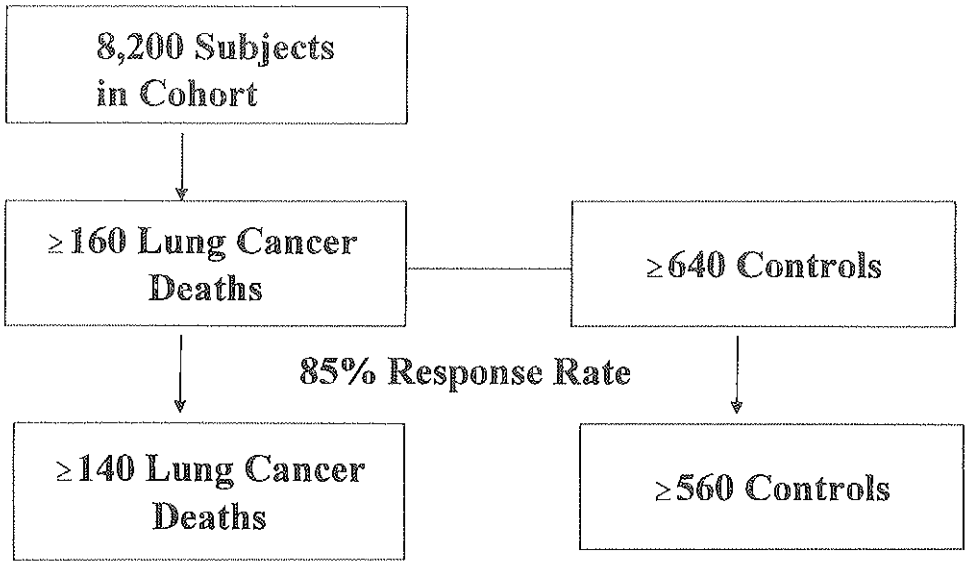
POTENTIAL CONFOUNDING FACTORS

- Age
- Gender
- Race/Ethnicity
- Cigarette Smoking
- Employment in High-Risk Occupations
- Asbestos Exposure
- Silica Exposure
- Pesticide Exposure
- Medical Conditions
- Diet

HISTORY OF CIGARETTE SMOKING

- Ever smoked cigarettes regularly
- Age started smoking
- Number of years smoked
- Usual lifetime amount smoked
- History of quitting

EXPECTED NUMBERS OF CASES AND CONTROLS



U.S. Non-Metal Miners: Industrial Hygiene Study

Daniel Yereb

Assessment of Current Exposure to Diesel Exhaust in Non-metal Miners and Surface Workers

Rebecca Stanevich, M.S.
Dan Yereb, M.S., Michael Attfield, Ph.D., Patty Schleiff, M.S.
National Institute for Occupational Safety & Health
Morgantown, WV

Mustafa Dosemeci, Ph.D., Debra Silverman, Sc.D., Jackie Prince, Ph.D.,
Nathaniel Rothman, M.D.
National Cancer Institute
Bethesda, MD

The National Institute for Occupational Safety and Health (NIOSH) and the National Cancer Institute (NCI) are conducting an epidemiologic study of mortality (with a focus on lung cancer) in non-metal miners exposed to diesel exhaust. NIOSH is responsible for the current assessment of diesel exhaust exposure in selected mines for the study. Current exposure assessments have been completed in two potash mines, two salt mines, one limestone mine and three trona mines. One potash mine remains to be sampled. These mines are located in New Mexico, Ohio, Louisiana, Missouri, and Wyoming.

To optimize the surveys at each mine, a variety of information was collected prior to the industrial hygiene survey. A one-day walk-through visit was held at each mine to familiarize the team leaders with the layout of the facility, the usage of diesel equipment, mine ventilation, active workings, shift schedules, etc. This walk-through afforded the company an opportunity to ask questions and become comfortable with the safety of our sampling procedures and the burden the survey would impose. During each survey, both personal and area sampling was conducted and had to be planned for during the walk-through visit.

Personal Sampling

The goal of personal sampling was to collect an adequate number of samples to represent a majority of the occupations both underground and on the surface. In some mines the number of occupations was very limited; in others, we knew that there would be a large number of occupations. Therefore, prior knowledge of the mining environment was essential in developing the sampling strategy. Sampling every occupation was not usually possible, so a good knowledge of mine-specific activities permitted us to group occupations when necessary. Prior knowledge of employee shift schedules were essential in developing a mine-specific sampling strategy, especially for planning the necessary equipment and samplers required for the industrial hygiene survey.

Each miner wore a sampler which measured elemental carbon and Palmes dosimeters which measured oxides of nitrogen. Our goal was to collect 40 - 50 personal samples per day. Experience has demonstrated that very few surface workers, even those exposed to diesel equipment have significant or even detectable levels of exposure to elemental carbon. Therefore, personal sampling of surface workers was restricted to only two days and was primarily focused upon those workers with potential diesel exposures. Underground workers were sampled during one or more shifts, over a five day period. Our preference was to measure two different workers in the same occupation, as opposed to measuring one person

on two different days. We also tried not to sample any one worker more than two times, simply due to the burden imposed upon him/her by the sampling equipment.

Area Sampling

The goal of area sampling was to develop correlations between our three primary surrogates of diesel exposure (elemental carbon, submicrometer particulate, and submicrometer combustible particulate) and the secondary surrogates (total dust, respirable dust, oxides of carbon, and oxides of nitrogen). These surrogates were selected because: they measure diesel exhaust exposure; have been included in prior studies (including a large study of seven of the mines, conducted in 1976 by MESA); are in MSHA's metal/non-metal compliance sampling database; and are readily measurable. Sulfur dioxide, for example, was included in the feasibility study conducted in 1992, but because the method was not sensitive enough, it was eliminated from the current industrial hygiene surveys.

Typically, six area sampling packages were placed in pre-selected areas for three of the five sampling days. On the remaining two days, two of the packages were placed on the surface, leaving four to be placed underground. Since the primary goal of the area sampling was to develop correlations between the various surrogates, the sample packages were placed in locations having a wide range of exposures. Our goal was to place about 25% in high exposure areas, 25% in low and 50% in the middle range. For this reason, the area samples did not necessarily provide representative data applicable to any particular job, working area, or the mine as a whole.

Our sampling packages included a variety of samplers. We measured carbon (elemental and organic) in three size fractions: total (open face), respirable (cyclone), and submicrometer (single-stage impactor). Particulates were measured in the same size range and using the same types of samplers. We also measured oxides of carbon using long-term colorimetric tubes, both active and passive. Nitrogen oxides were measured using TEA (triethanolomine) tubes and Palmes dosimeters. During two of the five sampling days, each of our area sampling packages also included an 8-stage impactor, metals sample, silica sample, asbestos sample and polynuclear aromatic hydrocarbon samples.

Sampling in an underground environment presents a host of problems not usually faced by the industrial hygienist. Foremost among these problems is the ventilation. Large quantities of air are forced through most mines. Due to the mine design, this volume of air tends to swirl and eddy. Even in the relatively small area being sampled, these ventilatory variations can cause disparity between side-by-side samples. Care must be taken in the placement of samplers to reduce this effect. In addition, the use of 10 - 15 pumps in this small area creates a ventilation pattern of its own, and, in some cases, a starvation effect. To reduce this effect, a sampling system was developed that oriented all of the samplers in the same direction, spaced them apart from one an other, and moved the pumps farther away from the sampling heads than we have done in the past. This has been very effective in reducing some of the sampling error seen in previous studies. Other challenges to sampling in an underground environment will be discussed in the presentation.

Currently, the industrial hygiene surveys have been completed in eight mines. Reports on these surveys are being sent to each mine as they become complete. We anticipate that the data generated from these surveys will become available to the public in the near future.

CURRENT EXPOSURE ASSESSMENT of DIESEL PARTICULATE IN NON-METAL MINES

Dan Yereb
Rebecca Stanevich
National Institute for Occupational Safety and Health
Field Studies Branch

Epidemiological Study

- Cohort Study
- Case-Control
- Historical Exposure Assessment
- Current Exposure Assessment

STUDY DESIGN

- Assess current levels of primary (EC) and other surrogates at each mine
- Conduct mine specific correlation studies between the levels of the primary surrogates and historical (NO_x, dust levels) surrogates
- Confirm low levels of potential confounders, e.g. silica, asbestos, radon

EXPOSURE ASSESSMENT OVERVIEW

- Mine Information/On-site
- Sampling Strategy
- Sampling Methods
- Sample Analysis

MINE INFORMATION

- Surface/underground maps
- Number of active working sections
- Types of diesel equipment
- Shift schedule
- Transportation arrangements

SAMPLING STRATEGY

- Provide estimates of current exposures to diesel exhaust contaminants through area and personal measurements

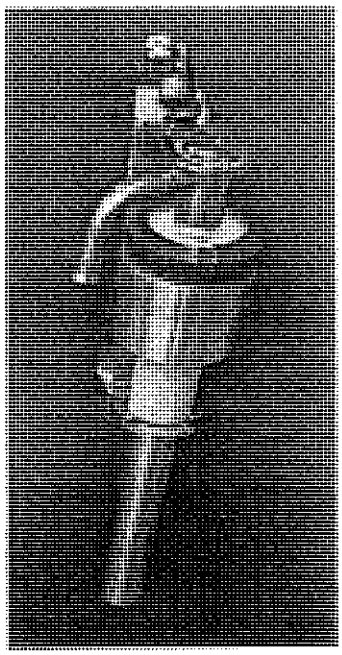
- Provide comparisons between elemental carbon and surrogates with historical measures

PERSONAL SAMPLING

- Obtain exposure information for each occupation
  - groups that have no historical exposure information

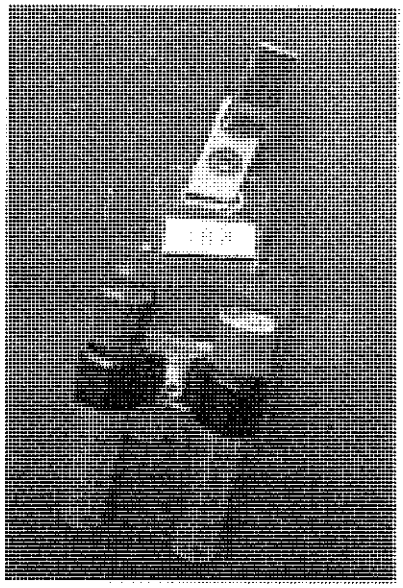
PERSONAL EXPOSURE MEASUREMENTS

- Elemental Carbon
  - Elemental
  - Organic
  - Total
- Palmes Dosimeter
  - NO
  - NO2



PERSONAL EXPOSURE MEASUREMENTS

- Elemental Carbon
  - Elemental
  - Organic
  - Total
- Palmes Dosimeter
  - NO
  - NO2



AREA SAMPLING

- Provide estimates of current exposures to diesel exhaust contaminants
  - selection of sampling method
  - evaluation of department/job combinations
  - types of diesel equipment

AREA SAMPLING

- Provide comparisons between elemental carbon and surrogates with historical measures
  - carbon monoxide, carbon dioxide
  - nitric oxide, nitrogen dioxide
  - total dust
  - respirable dust

AREA EXPOSURE MEASUREMENTS

- Elemental Carbon
- Submicrometer Combustible Dust
- Particulates
- Personal Impactor
- CO/CO2 (passive)
- CO/CO2 (active)
- NO/NO2 (TEA)
- NO/NO2 (Palmes)
- PAH
- Nitro-PAH

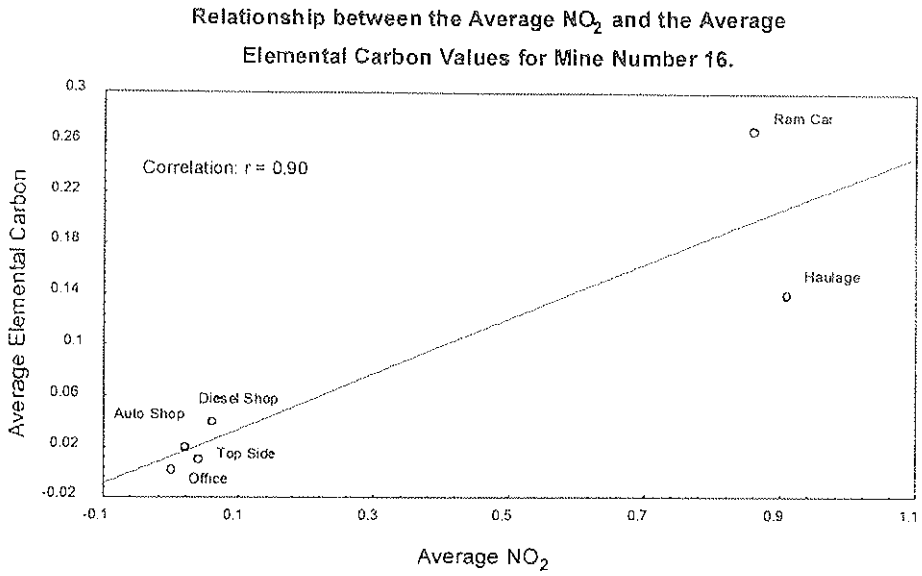
SECONDARY EXPOSURE MEASUREMENTS

- Real Time Measurements
  - Oxides of Nitrogen
  - Oxides of Carbon
  - Datalog/video overlay

Stratification of DEP
Micro-orifice uniform deposit impactor (MOUDI)

Confounders

- Silica
- Asbestos
- Radon
- Metals



AREA LOCATION

Surface

Low Exposure	Range	ND - 50 $\mu g/m^3$

Underground

Low Exposure	Range	ND - 100 $\mu g/m^3$
Medium Exposure	Range	100 - 300 $\mu g/m^3$
High Exposure	Range	> 300 $\mu g/m^3$

SURVEY MINES

CHALLENGES

- Selection of Occupations/Workers

CHALLENGES

- Selection of Areas

CHALLENGES

- Sample/Data Management

CHALLENGES

- Sample Analysis

SAMPLE ANALYSIS

- EGA by Thermal-optical analyzer
- Gravimetric
- Spectrophotometric
- Colorimetric
- Gas Chromatography
- Nitrogen Chemiluminescence
- X-Ray Diffraction
- Phase Contrast Microscopy
- Polarized Light Microscopy
- ICP
- Counting GS

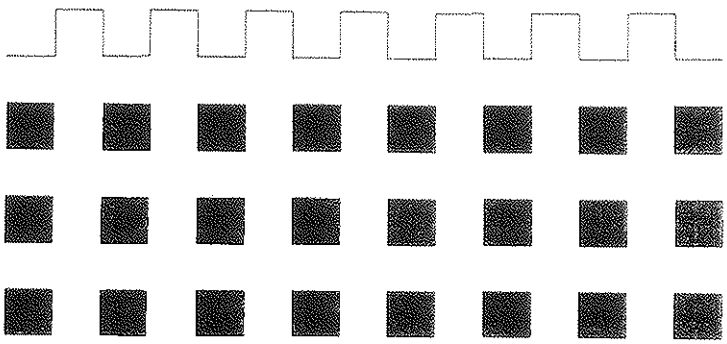
LOCATION		DAY 1	
AREA 1	*AREA1*	☐ SURFACE	☐ UNDERGROUND

DATE	MINE #

SAMPLE #	BAR CODE	SAMPLE TYPE	FLOW RATE	PUMP NO.	TIME ON	TIME OFF	VOLUME (lpm)
50232-ECT	*50232-ECT*	Bemerdal Carbon Total	1.0 lpm				
61721-ECR	*61721-ECR*	Bemerdal Carbon Respirable	1.7 lpm				
90352A-TEA	*90352A TEA*	TEA Molecular Sieve	0.025 lpm				
90352B-TEA	*90352B TEA*	TEA Molecular Sieve	0.025 lpm				
70652A-ECS	*70652A ECS*	Bemerdal Carbon Submicron	1.0 lpm				
70652B-ECS	*70652B ECS*	Bemerdal Carbon Submicron	1.0 lpm				
580-MCE	*580-MET*	Metals	2.0 lpm				
354-PAH	*354-PAH*	Poly Aromatic Hydrocarbon	2.0 lpm				
974546-TD	*974546-TD*	Total Dust	1.0 lpm				
974419-RD	*974419-RD	Respirable Dust	1.7 lpm				
40364-SD	*40364-SD*	Submicrometer Dust	1.0 lpm				
81811-PT	*81811-PT*	Pemex Tube	Passive				
10170-ID	*10170-IDT	Impactor Dust	2.0 lpm				

SAMPLE #	BAR CODE	GAS TYPE	FLOW RATE	PUMP NO.	TIME ON	TIME OFF	PPM HOURS
00360A-CO2	*00360A CO2*	Carbon Dioxide	0.02 lpm				
00360B-CO2	*00360B CO2*	Carbon Dioxide	0.02 lpm				
00222-CO2	*00222-CO2*	Carbon Dioxide	Passive				
00422-CO	*00422-CO*	Carbon Monoxide	Passive				
00750-CO-10	*00750-CO 10*	Carbon Monoxide (10 ppm)	0.02 lpm				

Comments:



PERSONNEL		EQUIPMENT	DIESEL	ELECTRIC	% TIME IN USE
NAME	JOB TITLE/OCCUPATION	UNDERCUTTER	○	○	
		JUMBO DRILL	○	○	
		ROOF BOLTER	○	○	
		SCALER	○	○	
		LHD	○	○	
		UTILITY	○	○	
		MAN TRIP	○	○	
		SKID STEER	○	○	
		POWDER BUGGY	○	○	
		FRONT END LOADER	○	○	
		DOZER	○	○	

CONCLUSIONS

- Mines have different exposures
- Diesel usage
- Correlations are different
- Job to job differences

JOB to JOB DIFFERENCES

Comparison of Average Personal Exposures to Elemental Carbon by Occupation

Comparison of Average Personal Exposures to Elemental Carbon by Occupation

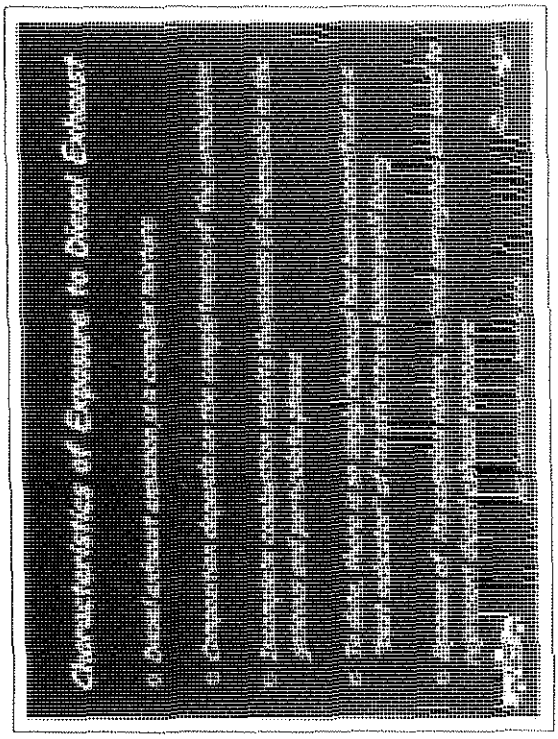
U.S. Non-Metal Miners: Historical Exposure Assessment

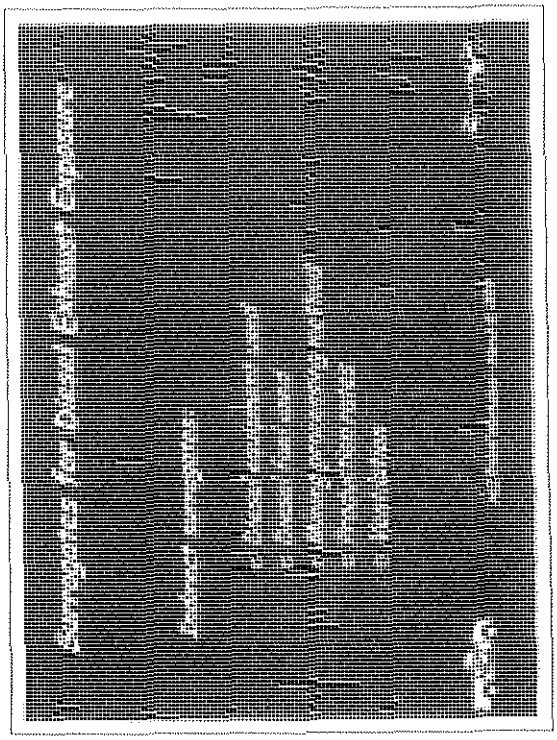
Mustafa Dosemeci

Retrospective Assessment of Exposure to Diesel Exhaust in a Cohort Mortality Study with a Nested Case-control Study of Lung Cancer among Non-metal Miners in the U.S.
Mustafa Dosemeci, Jackie Prince, Debra Silverman, National Cancer Institute; Rebecca Stanevich, Daniel J Yereb, Patricia S Schleiff, Michael Attfield, National Institute for Occupational Safety and Health.

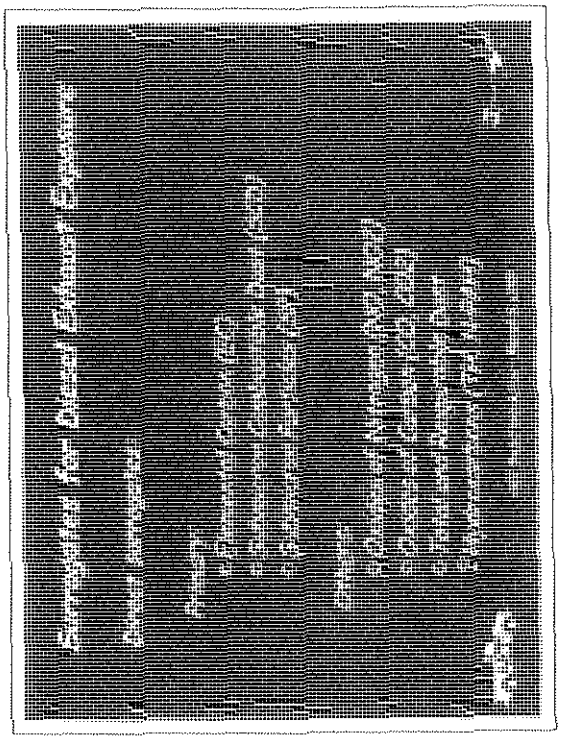
NCI in collaboration with NIOSH is developing a quantitative exposure assessment method to estimate retrospective exposure to diesel for 8,200 mine workers in ten non-metal mines in the U.S. Diesel exhaust is a complex mixture of combustion products, and the composition of the exhaust emissions depends on the completeness of the combustion. These incomplete combustion products comprise thousands of chemicals in the gaseous and particulate phases of the diesel exhaust. Because of the complex nature of the diesel exhaust, various surrogates are used to represent overall diesel exhaust exposure.We have identified two types of surrogates, direct and indirect, that are being used in the assessment of historical exposure to diesel exhaust. The direct surrogates provide quantitative information on one or more chemical components of the diesel exhaust and are obtained by direct measurement of the component, such as elemental carbon (EC), organic carbon, respirable combustible dust (RCD), diesel particulate matters (DPM), oxides of nitrogen, oxides of carbon, total dust, respirable dust, total hydrocarbons, nitrogenated polycyclic aromatic hydrocarbons, and polycyclic aromatic hydrocarbons. Indirect surrogates are the current and historical information on diesel exhaust exposure, such as types, number and horsepower of diesel equipment used, the amount of diesel fuel used, ventilation system, production process and other exposure-related information.

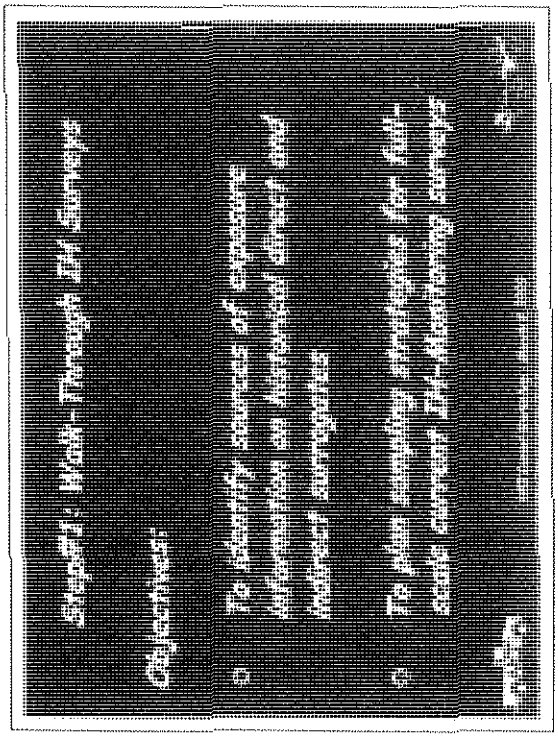
In this study, we have been focused on EC, RCD and DPM as the primary surrogates for diesel exhaust. We have conducted an extensive monitoring survey at each study mine to establish the relationship between these primary surrogates and the other direct and indirect surrogates of diesel exhaust exposure that were available historically. First, together with NIOSH industrial hygienists, we have conducted walk-through surveys at each study mine to collect historical exposure information on direct and indirect surrogates, using standardized exposure information abstraction tools. The initial standardization of original job titles and departments (work areas) has been carried out based on the information obtained from walk-through IH surveys and from personnel records. After the initial collection of the work histories, we identified preliminary unique mine/department/job title/calendar period (M/D/J/C) combinations using standardized department/job titles and historical information on the level of direct and indirect surrogates. Final combinations will be identified after the full scale work history collection is complete and will form the basis of our retrospective assessment of exposure to primary surrogates of diesel exhaust. The full scale IH monitoring survey at each mine has been conducted to measure the current levels of the surrogates and to conduct mine-specific correlation studies between the levels of primary surrogates and historical surrogates. Both current and historical exposure information is being documented in a computerized exposure assessment software program developed by NCI and NIOSH. Statistical calculations and individual estimates of intensity levels for each M/D/J/C combination are being calculated using this software program. After estimation of the intensity levels, various quantitative exposure indices (e.g., cumulative exposure, time-weighted cumulative exposure, average exposure, and highest exposure) will be calculated for each individual study subject in the cohort study.

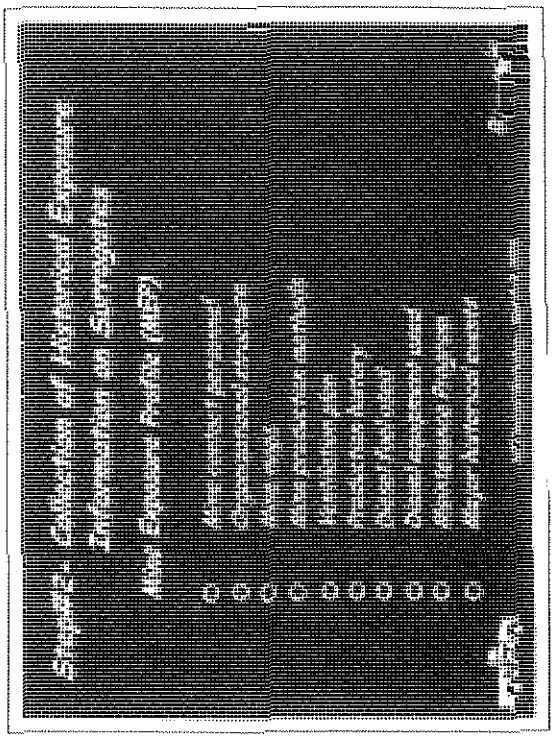


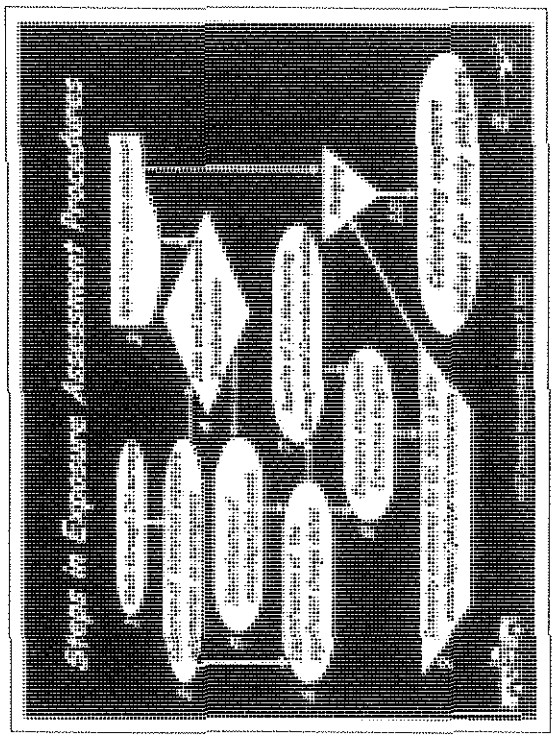


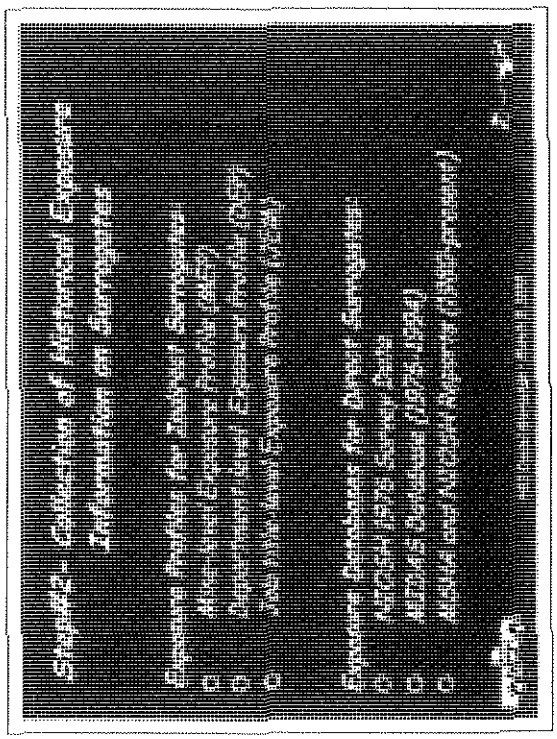

The Retrospective Assessment of Exposure to Diesel Exhaust
Andrew Dement, Ph. D.

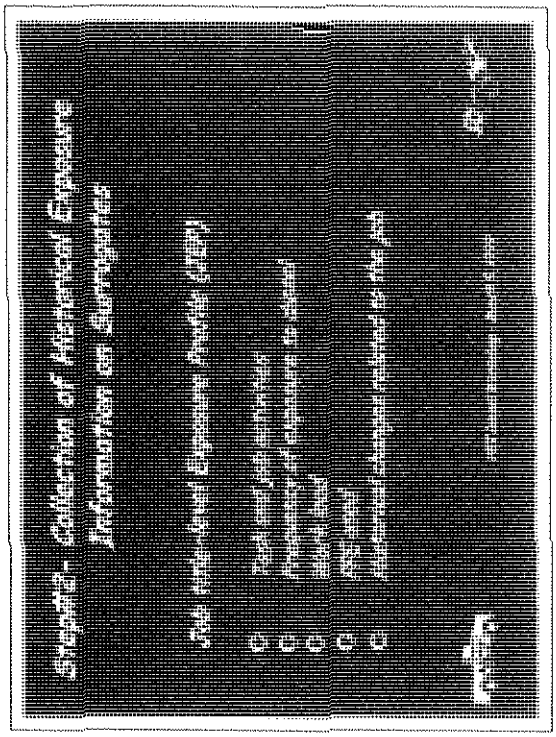


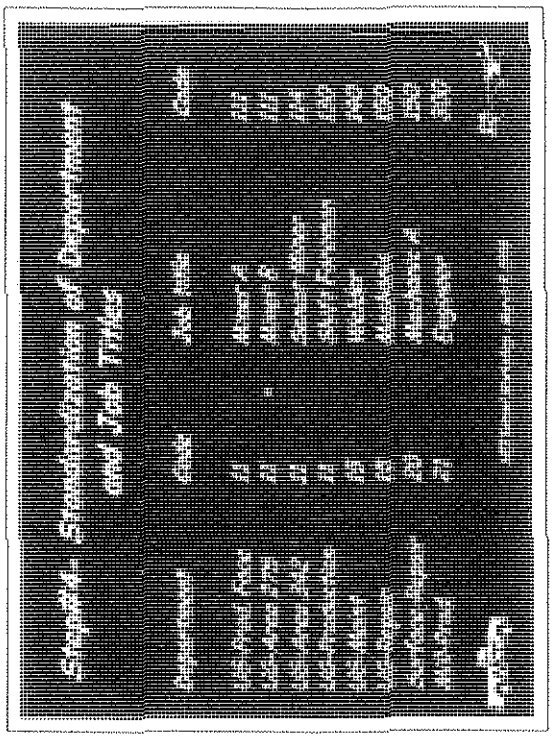


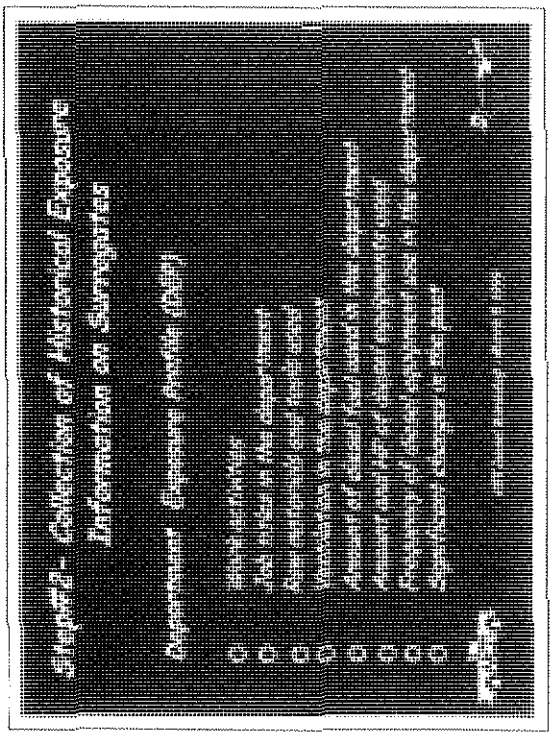


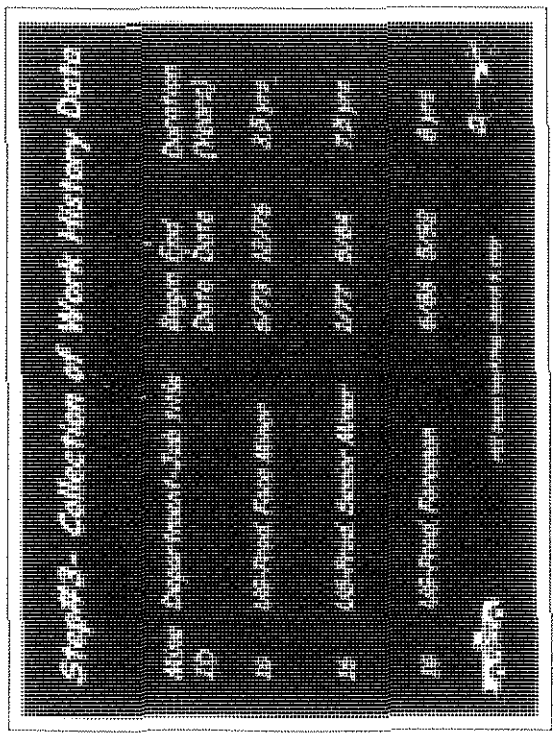


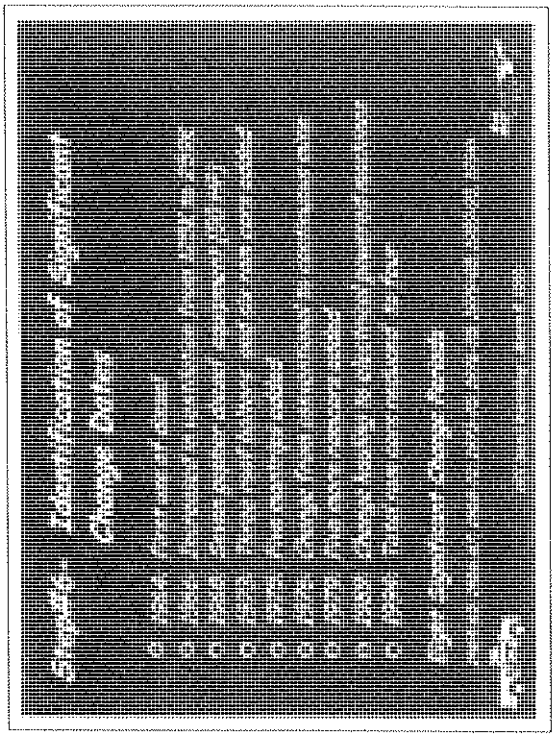


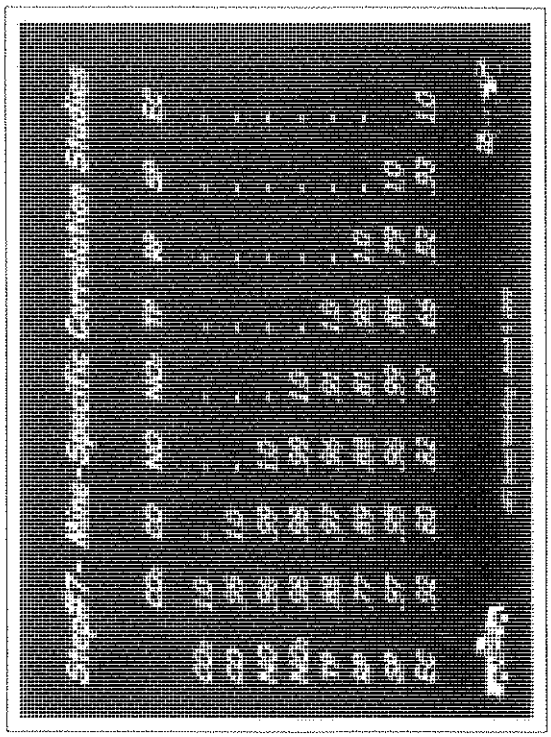


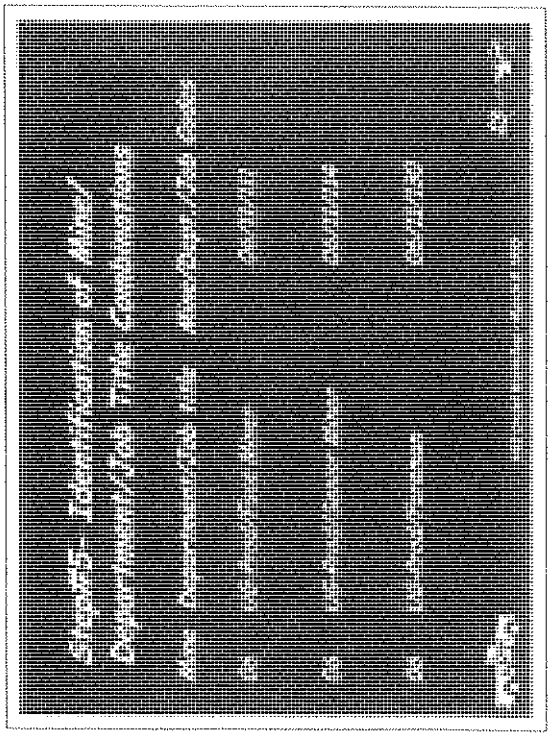


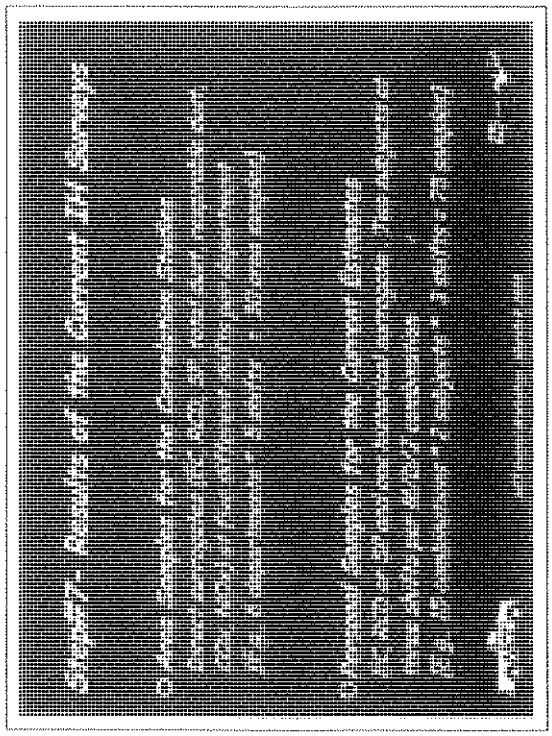


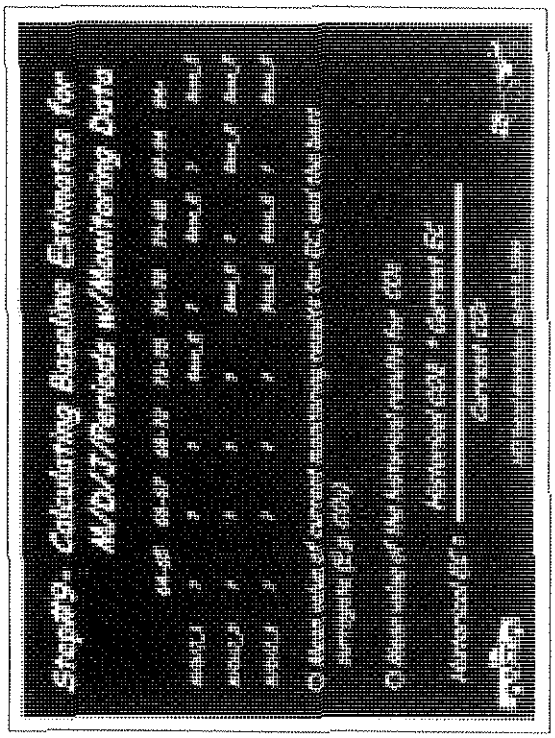


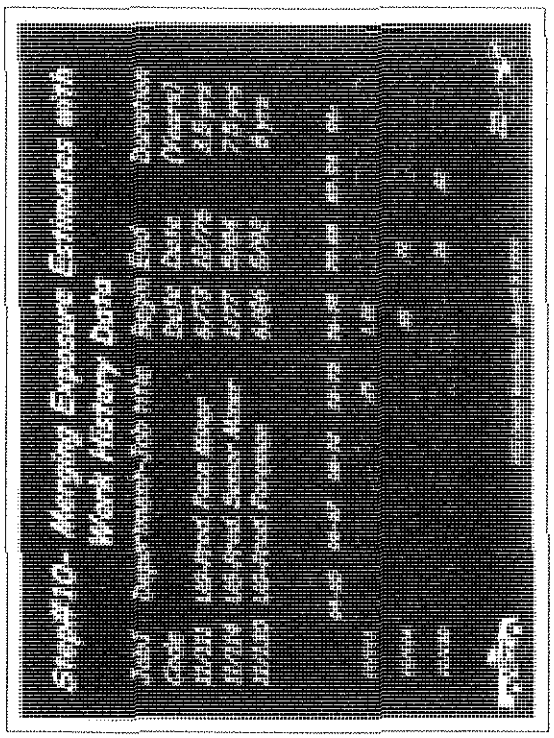


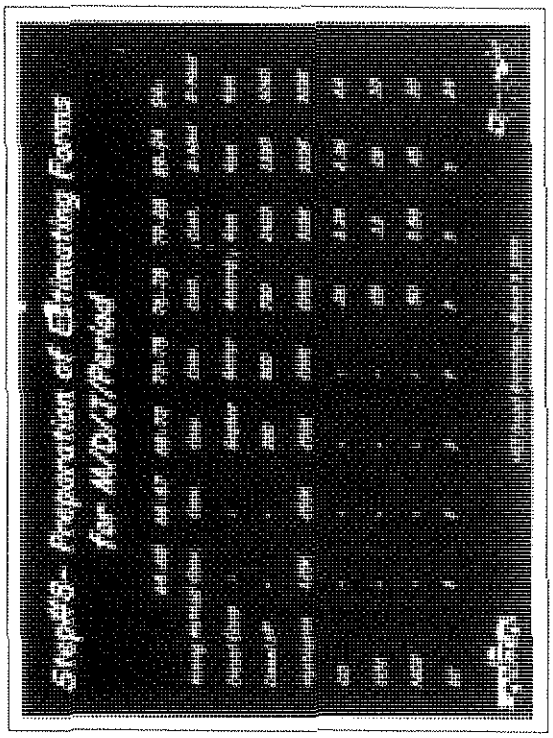


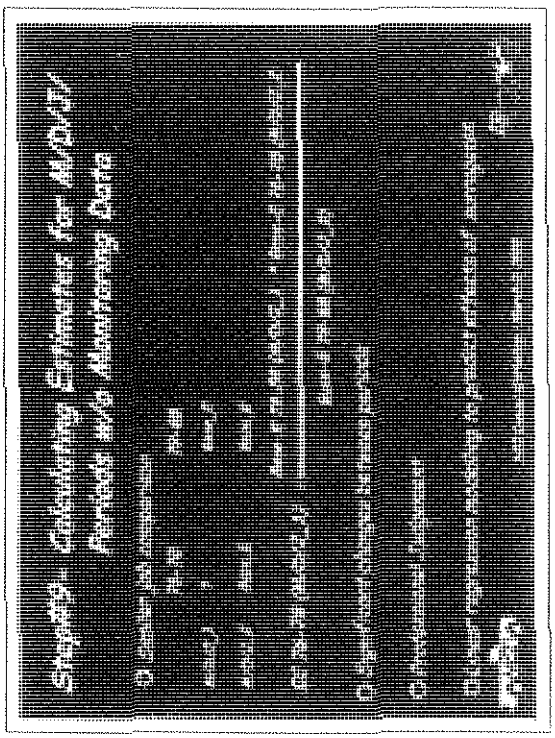












Step#10- Calculating Exposure Indices for study subjects

	64-65	66-67	68-72	73-75	76-78	79-88	89-94	94+
M/D/J_1				25	120			
M/D/J_2					65	72		
M/D/J_3						26	02	

M/D/I_1 : (.25 mg/M^3 * 2.5 yrs) + (1.2 mg/M^3 * 1 yr) = 1.83 mg/M^3-yrs

M/D/I_2 : (.65mg/M^3 * 2 yrs) + (.72 mg/M^3 * 5.5 yrs) = 5.26 mg/M^3-yrs

M/D/I_3 : (.26 mg/M^3 * 4.5 yrs) + (.02 mg/M^3 * 3.6 yrs) = 1.24 mg/M^3-yrs

Cumulative Exposure : 1.83 + 5.26 + 1.24 = 8.33 mg/M^3-yrs

Average intensity : (8.33 mg/M^3-yrs) / (19 yrs) = 0.44 mg/M^3

Step#10- Calculating Exposure Indices for study subjects

For historical exposure to EC, RCD and SP :

- Duration of exposure in years
- Cumulative Exposure in mg/M^3-yrs
- Average Intensity in mg/M^3
- Maximum Intensity in mg/M^3
- Other historical exposure indices

Future Activities Related to the Assessment of Historical Exposure to Diesel

- Complete documentation of exposure information for each M/D/J/Period combination in the study.
- Verify documented historical exposure information with local technical personnel in the study mines
- Estimate exposure levels of EC, RCD and SP for each M/D/J/Period combination

Future Activities Related to the Assessment of Historical Exposure to Diesel

- Verify estimates with local technical personnel in the study mines
- Calculate exposure indices to be used in the statistical analysis
- Conduct methodological studies to validate exposure assessment strategies used in the study

SESSION VII

Consideration of Health Endpoints Other Than Cancer in Future Risk Assessments of Diesel Emissions

Michael Lipsett, Chair

Bert Brunekreef

Thomas Sandström

David Diaz-Sanchez

The workshop's final session considered health outcomes other than lung cancer that might be associated with diesel exhaust exposure. Presentations included ongoing research on respiratory health in children, inflammatory airway effects, and human allergic responses.

Introduction

Michael Lipsett

DIESEL: OTHER OUTCOMES

- Which health outcomes should be considered for quantitative risk assessment?
- What research approaches would be most useful in providing relevant exposure-response data?

AMBIENT DIESEL PARTICLE CONCENTRATIONS

Various U.S.	1 - 3 $\mu g/m^3$
California	0.2 - 3.6 $\mu g/m^3$
Austria	11 $\mu g/m^3$
Urban hotspots	up to 15 $\mu g/m^3$
Occupational	Several $\mu g/m^3$ to >1 mg/m^3

DIESEL EXHAUST AS A COMPONENT OF PM10/ PM2.5

Ambient PM has been repeatedly linked with:

- Daily and long-term cardiopulmonary mortality
- Hospital and emergency room visits for cardiac and respiratory illness
- Acute and chronic respiratory symptoms
- Transient lung function decrements
- School absenteeism
- Medication use and symptoms in asthmatics

DIESEL EXHAUST: ACUTE EFFECTS

- Symptoms reported include eye and mucous membrane irritation, cough, phlegm, dyspnea, headache, light-headedness, nausea, odor annoyance
- Cross-shift changes in lung function
- Inflammatory changes in bronchoalveolar lavage fluid after controlled exposures

DIESEL EXHAUST: CHRONIC EFFECTS

- Human occupational epidemiological studies generally not informative because of cross-sectional designs
- At high levels of exposure, animal studies indicate pathologic changes consistent with chronic inflammation
- DEPs exert numerous effects on allergic inflammation, and as allergy adjuvant in animals and humans

DIESEL - PRIOR RISK ASSESSMENTS FOR NONCANCER EFFECTS

- WHO, U.S. EPA and Cal/EPA all calculated chronic RfCs or guidance values based on animal toxicology studies
- WHO guidance values and benchmark concentrations based on chronic alveolar inflammation, impaired lung clearance and hyperplastic lesions:
- WHO range = 0.9 - 14 $\mu g/m^3$

DIESEL - PRIOR RISK ASSESSMENTS FOR NONCANCER EFFECTS

- U.S. EPA and Cal/EPA both relied on Ishinishi et al. (1988) rat study
- U.S. EPA used NOAEL + uncertainty factor to arrive at Rfc of 5 $\mu g/m^3$
- Cal/EPA used benchmark dose approach based on hyperplastic lesions in female rats: range 2 - 21 $\mu g/m^3$, recommended 5 $\mu g/m^3$

Environmental Exposure and Respiratory Health of Children

Bert Brunekreef

Environmental diesel exhaust exposure and respiratory health of children in the Netherlands

Bert Brunekreef, PhD, Nicole Janssen, PhD, Patricia van Vliet, MSc, Francee Aarts, MD
University of Wageningen, The Netherlands

The contribution of motorized traffic to air pollution is widely recognized, but relatively few studies have looked at the respiratory health status of subjects living near busy roads.

In a study conducted in 1995, we studied children in six areas located near major motorways in The Netherlands. Schools situated at less than 1,000 m. from major freeways in the Province of South Holland were asked to participate. The selected freeways carry between 80,000 and 150,000 vehicles per day. Separate counts for truck traffic indicated a range from 8,000 - 17,500 trucks per day. On a total of 13 schools, 1,498 children were asked to participate. Lung function was measured, and exposure to traffic-related air pollution was assessed using separate traffic counts for automobiles and trucks, and measurements of air pollution conducted in the schools of the children. Lung function was associated with truck traffic density, but less so with automobile traffic density. The association was stronger in children living closest (< 300 m.) to the motorways. Lung function was also associated with the concentration of Black Smoke, measured inside schools, as a proxy for diesel exhaust particles. The associations were stronger in girls than in boys. Chronic respiratory symptoms reported in the questionnaire were analysed with logistic regression. Distance of the home from the freeway and traffic intensity were used as exposure variables. Cough, wheeze, runny nose and doctor-diagnosed asthma were significantly more often reported for children living within 100 m. from the freeway. Truck traffic intensity in particular was found to be associated with chronic respiratory symptoms. The results suggest that exposure to traffic-related air pollution, in particular diesel exhaust particles, may lead to reduced lung function, and increased respiratory symptoms, in children living near major motorways. The results of this study have been published in recent years (Brunekreef et al., 1997, van Vliet et al., 1997, Roorda-Knape et al., 1998).

The results of this first study prompted us to implement a new study to look into these issues further. The new study was conducted in 1997 and 1998, and results are currently being analysed. In the new study, we selected 24 schools all located within 400 m. of busy motorways. All roads in the Netherlands are equipped with automatic counters, located between all exits so that for each stretch of road, the exact number of vehicles passing through is known. Moreover, by measuring the length of the passing vehicles, they are also being classified into light traffic (vehicles less than 5.1 meters) and heavy traffic (vehicles longer than 5.1 meters). This corresponds closely to cars and trucks respectively. In the Netherlands, practically all trucks have diesel engines, whereas only about 11% of the passenger car

fleet has diesel engines. In view of the much smaller diesel exhasut emissions of passenger cars with diesel engines than of trucks, the traffic counts provide an opportunity to separate gasoline exhaust from diesel exhaust fumes. The mean weekday car count on the roads we studied was 89,544 (range 30,399 – 155,656). The mean weekday truck count was 13,146 (range 5,190 – 22,326). The correlation between car and truck counts was low (0.31).

We measured PM2.5, filter reflectance, NO_2 and VOC including benzene inside and outside of all schools. In selected locations, we measured elemental carbon, particle composition (XRF for elementa and GC for PAH). We questioned the children using the symptom questionnaire developed by the International Study on Asthma and Allergy in Children (ISAAC). We measured serum IgE and skin reactivity to common allergens to document the atopic status of the children. We measured lung function using heated pneumotachometers. We also measured bronchial reactivity to hypertonic saline. Altogether, about 2,500 children participated, although not all of these particpated in all modules of the study.

Data are currently being analyzed. First results indicate a close correlation between filter reflectance and EC, suggesting that the simple filter reflectance measurement is a good proxy for EC, which in turn is a proxy for diesel exhaust. NO_2 concentrations were found to depend on total traffic density, distance from the road and percentage of time the school was downwind from the road during the measurement weeks. The level of filter reflectance was primarily related to the density of truck traffic, and to distance from the road and percentage of time downwind. These findings are similar to the findings of our earlier study.

Health data analysis is still very preliminary. First unadjusted analyses suggest a relationship between several respiratory symptoms and truck (but not car) traffic density, as in our first study. First unadjusted analyses of lung function fail to show that car or truck traffic density is associated with lower lung function. In view of the preliminary nature of these analyses, they should not be interpreted as supporting or refuting an effect of traffic exhaust on respiratory health of children living near busy freeways.

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Brunekreef B, Janssen NAH, Hartog J de, Harssema H, Knape M, Vliet P van.
Air pollution from truck traffic and lung function in children living near motorways.
Epidemiology 1997; 8: 298-303

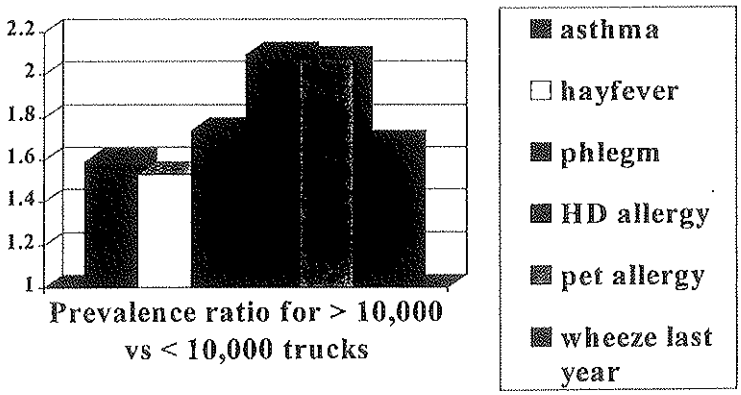
Roorda-Knape MC, Janssen NAH, Hartog JJ de, Vliet PHN van, Harssema H, Brunekreef B.
Air pollution from traffic in city districts near major motorways.
Atmosf Environ 1998; 32: 1921-1930

Vliet P van, Knape M, hartog J de, Janssen NAH, Harssema H, Brunekreef B.
Motor vehicle exhaust and chronic respiratory symptoms in children living near freeways.
Environ Research 1997; 74: 122-132

Study design

- 24 schools, located near freeways with varying traffic density
- monitoring of PM2.5, BS, NO_2, Benzene indoors and outdoors; EC, PAH and elements (XRF) in selected samples
- health measurements in approx. 2,500 children (7-12 yrs old) following ISAAC-2 protocols

Association between truck traffic and symptoms



Background...

- Several studies suggest that living close to busy roads is associated with impaired respiratory health
- A study from the Netherlands suggests that truck traffic density (diesel exhaust) on freeways is associated with reduced lung function, and increased prevalence of wheeze in school children

Study design

- 24 schools, located near freeways with varying traffic density
- monitoring of PM2.5, BS, NO_2, Benzene indoors and outdoors; EC, PAH and elements (XRF) in selected samples
- health measurements in approx. 2,500 children (7-12 yrs old) following ISAAC-2 protocols

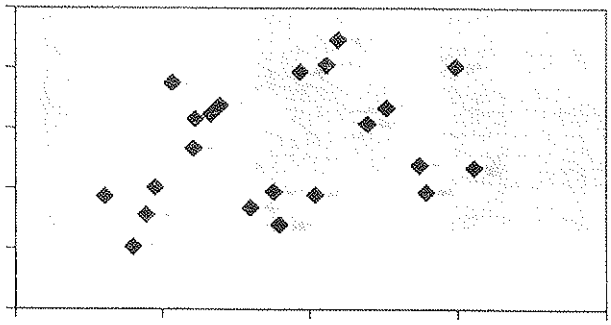
Methods (exposure)

- PM2.5: Harvard Impactor
- BS: reflectance measured of PM2.5 filters
- NO_2: Palmes' tubes
- Benzene: charcoal tubes, GC
- EC: thermographic (VDI-2465)
- PAH: GC

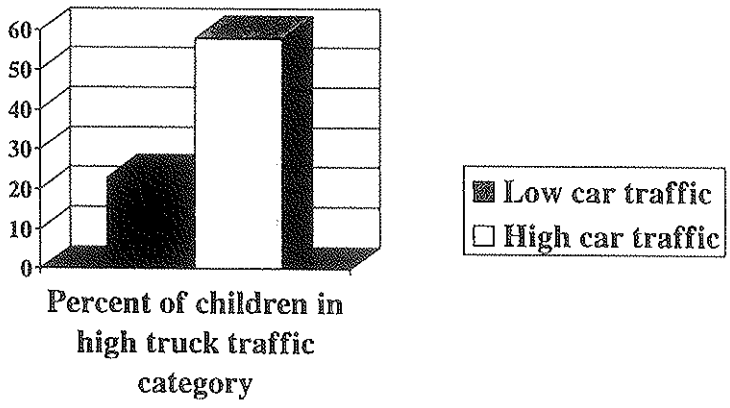
Methods (health)

- Symptoms by ISAAC questionnaire
- Lung function by heated pneumotachometer
- BHR by hypertonic saline challenge
- Sensitisation by SPT (ALK) and total and specific IgE (Pharmacia)

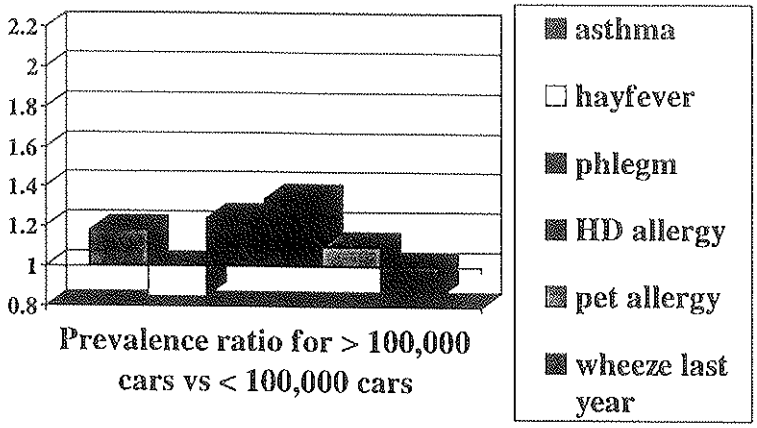
Truck (Y) and car (X) traffic density of freeways near participating schools



Association between car traffic and truck traffic in restricted data



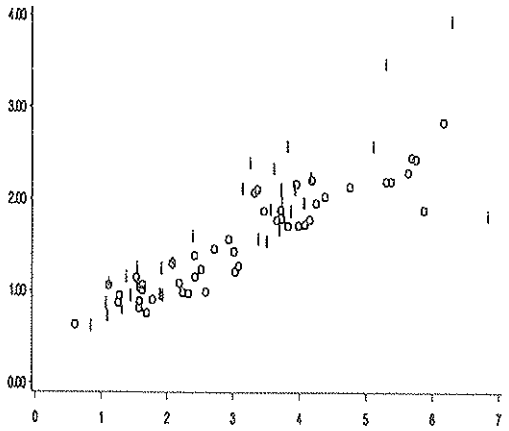
Association between car traffic and symptoms



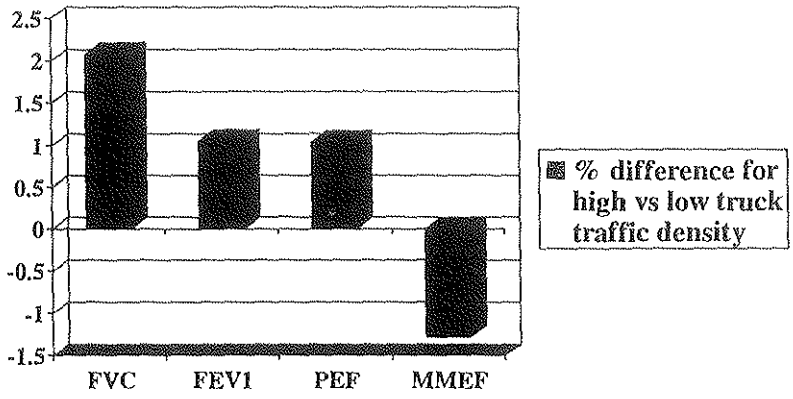
Relation between PM2.5 absorbance (Y) and EC concentration (X)

O = outdoor
R = 0.92

I = indoor
R = 0.85



Association between truck traffic and lung function



Mean air pollution concentrations

- PM2.5 outdoors: 24.8 $\mu g/m^3$
- PM2.5 indoors: 23.0 $\mu g/m^3$
- Absorbance outdoors: 1.60 m^{-1}
- Absorbance indoors: 1.86 m^{-1}
- NO_2 outdoors: 39.2 $\mu g/m^3$
- NO_2 indoors: 19.1 $\mu g/m^3$

Distance of school to freeway, and traffic density

- Distance to freeway (m): 209 (47 - 377)
- Car traffic/day 89,544 (30,399 - 155,656)
- Truck traffic/day 13,146 (5,190 - 22,326)

Determinants of PM2.5

	Outdoors (estimate, se):	Indoors (est, se):
10k trucks	4.23 (0.83)	3.40 (1.57)
50 k cars	-0.93 (0.50)	0.16 (0.95)
ln(distance)	-2.08 (0.56)	-2.36 (1.08)
% downwind	-0.42 (0.84)	1.48 (1.15)

Caution!!!

- Results are very preliminary at this stage
- Associations with symptoms unadjusted
- No difference between boys and girls
- Not explained by response rate per school
- Associations with lung function only adjusted for height, weight, gender, age

Some restrictions in preliminary analyses:

- Children & parents born in the Netherlands
- Schools located at less than 200 m from freeway
- Distance of home to freeway not yet available

Determinants of Absorbance

	Outdoors (estimate, se):	Indoors (est, se):
10k trucks	0.23 (0.07)	0.21 (0.12)
50 k cars	0.02 (0.04)	0.11 (0.07)
ln(distance)	-0.22 (0.05)	-0.32 (0.08)
% downwind	0.25 (0.04)	0.36 (0.09)

Determinants of NO_2

	Outdoors (estimate, se):	Indoors (est, se):
10k trucks	2.69 (2.38)	-3.09 (2.49)
50 k cars	2.66 (1.45)	4.10 (1.51)
ln(distance)	-2.65 (1.57)	-0.67 (1.72)
% downwind	5.87 (2.26)	3.31 (1.22)

Airway Inflammation by Diesel Exhaust

Thomas Sandström

INFLAMMATORY EFFECT OF DIESEL EXHAUST ON HUMAN AIRWAYS

Thomas Sandström.
Dept of Respiratory Medicine and Allergy, University Hospital, Umeå, Sweden;

Particulate matter (PM) pollution is of considerable concern for airway health. Diesel exhaust (DE) is an important source of PM pollution. Airway effects have been demonstrated in work place- and epidemiological studies. Airway inflammation by ultrafine particles and DE, have been well established by the work of Oberdörster, Mauderly and colleagues, as well as several other groups.

More detailed information as to, to what extent and through what mechanisms humans respond to DE, has long been lacking. Through multidisciplinary collaboration, it was therefore developed a carefully designed and validated exposure set up, which has been used for controlled studies of DE effects in humans. Following basic technology evaluations, symptoms and bronchoconstrictive effects have been studied in healthy subjects. This was followed by the addition of bronchoscopy studies evaluating airway inflammatory effects of DE. Reactive airway effects were found involving neutrophils, mast cells and suppression of alveolar macrophage phagocytic functions.

Through collaboration of UK-Scandinavian groups, the mapping of the respiratory responses to DE has taken additional steps. Through antioxidant measurements the oxidative stress caused by the particles within the human airways have been confirmed. Recently it has been shown that exposure to a DE concentration of 300 $\mu g/m^3$ PM_{10} induced a pronounced airway inflammation in healthy subjects. This was reflected not only in bronchial washes and BAL hut even more so in the bronchial mucosa, as reflected in immunostained biopsies. The use of PCR, and immunostainings for cytokine proteins, cell identity, activation, reactive enzymes and adhesion molecule expression have increased the understanding of the mechanistic aspects. The usefulness of nasal lavages and induced sputum, as complementary and less invasive techniques to study DE effects, have been confirmed.

Since the level of PM 300 $\mu g/m^3$ is a relatively high busy street curb side concentration, it was of importance to address whether the effects would also be present at lower levels, or restricted only to higher. To address this 25 healthy subjects and 14 mild asthmatics were exposed to DE (100 $\mu g/m^3$ PM_{10}) and air for 2 hours, in an exposure chamber on two separate occasions, in randomised sequence. Bronchoscopy with bronchial wash (BW), bronchoalveolar lavage (BAL) and biopsy sampling were performed six hours after exposure. Biopsies were processed in GMA and immunostained for cells and vascular adhesion molecule expression. Data for healthy subjects were completed at the time of abstract submission.

It was found that also exposure to diesel exhaust containing PM 100 $\mu g/m^3$ induced inflammatory reactions in the airways of healthy subjects. The acute cytokine and

chemokine presence with IL-6 and IL-8, together with enhanced expression of the vascular adhesion molecules P-selectin and VCAM-1 in the biopsies, suggest an early state of recruitment of inflammatory cells. Mechanisms for neutrophil migration into the airways were present, though not fully developed at 6 hours after exposure. The inflammatory changes showed qualitative similarities, but were less pronounced than in the 300 $\mu g/m^3$ diesel study, performed with identical protocol. The profile of the inflammatory markers suggests a slower development of airway inflammation after 100 μg DE PM/m^3, than after 300 $\mu g/m^3$. A later time point of bronchoscopy, 12-18 hours after exposure, may have reflected a more established state of inflammation. The material from the similarly investigated asthmatics is expected to yield additional understanding of diesel exhaust effects in this potentially more sensitive group.

In summary, studies using controlled chamber exposures with DE in human subjects give support to the epidemiological studies, suggesting PM pollution to be of importance for airway health. The reactive and irritative effects within the airways found in healthy subjects occur after moderate levels of DE PM. A level below which no biomedical effects occur in healthy individuals has not yet been identified. Information on sensitive groups behaviour are furthermore of importance to clarify.

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Rudell B, Wass U, Östberg Y, Hörstedt P, Ranug U, Lindhal R, Sunesson A-L, Levin J, Sandström T. Efficacy of filters to reduce acute health effects of diesel exhaust in. Occup Environ Med, In press.

Airway inflammation by Diesel exhaust

Thomas Sandström
Dept of Respiratory Medicine & Allergy
Univ Hospital of Umea
Sweden

PM pollution

- Are there any effects within the airways and vascular system corresponding to the epidemiological findings ?

Chamber exposures

Selected populations

healthy, allergic, asthma, COPD

Exposure situation mimicking real life

Controlled exposure concentrations

(Rudell *et al,* Int Arch Occup Environ Health 1994)

Predetermined work load / ventilation rate

Randomised sequence - filtered air / air pollutant

PM and Airway Inflammation

- G Oberdorster
  - Ultrafine particles

- J Mauderly
  - Lung damages by diesel exhaust

DE set-up

- Exposures validated
- Constant concentrations
- Rapid steady state
- Components and ratios kept
- Particle size kept

Rudell et al Int Arch Occup Health 1994

Evaluation of health effects

Symptoms
Lung function test
Nasal lavage
Bronchoalveolar lavage
Bronchial biopsies
Induced sputum
Peripheral blood

Diesel exhaust *300* $\mu g/m^3$ PM_{10}

Material & methods

- Eight healthy subjects
- One-hour exposure
- *BAL* 18 hours after end of exposure

Rudell *et al*, J Aerosol Sci 1990

Diesel exhaust *300* $\mu g/m^3$ PM_{10}

Results

- Bronchial wash
  - ↓ mast cells
- BAL
  - ↑ PMNs
  - ↓ *in-vitro* phagocytosis by AM

Rudell *et al*, J Aerosol Sci 1990

Diesel exhaust *300* μg/m^3 PM_{10}

Results

- Symptoms
  unpleasant smell, eye and nasal irritation
- Lung function (FEV_1, FVC)
  unaffected

Rudell *et al,* Int Arch Occup Environ Health 1994

Diesel exhaust *300* μg/m^3 PM_{10}

- Three randomised exposures in all subjects
- Air, *filtered* and *unfiltered* diesel exhaust
- *Particle trap*
- 12 healthy subjects
- *Bronchoscopy with BAL* 18 hours after end of exposure

Rudell *et al*, Occup Environ Med 1996

Diesel exhaust *300* μg/m^3 PM_{10}

Results *without* particle trap

- Symptoms
  - ↑ unpleasant smell, eye and nasal irritation
- Lung function
  - ↑ airway resistance
- BAL
  - ↑ PMNs
  - AM
  - AM phagocytosis in-vitro
  - CD3/CD25 +

Rudell *et al*, Occup Environ Med 1996 + in press

Diesel exhaust *300* μg/m^3 PM_{10}

Results *with* particle trap

- Despite the 46 % reduction in particle numbers, effects on symptoms, lung function and airway inflammation were *not* significantly attenuated

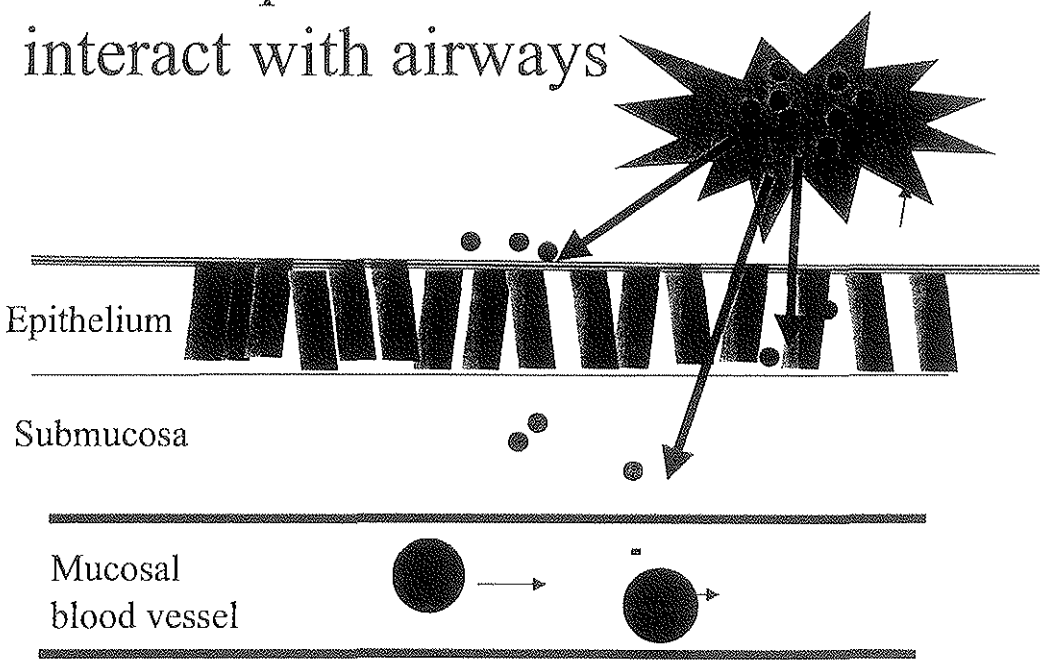
Rudell *et al*, Occup Environ Med 1996 + in press

Diesel exhaust exposure

- 15 healthy non-atopic subjects
- 300 μg/m^3 particles for one hour vs air
- *Bronchial biopsies* and *BAL* six hours after end of exposure

Salvi *et al,* Am J RCCM, in press

Exhaust particles interact with airways



Diesel exhaust *300* $\mu g/m^3$ PM_{10}

- Oxidative stress

↑

- PCR on biopsies

  IL-8 and IL-5

↑

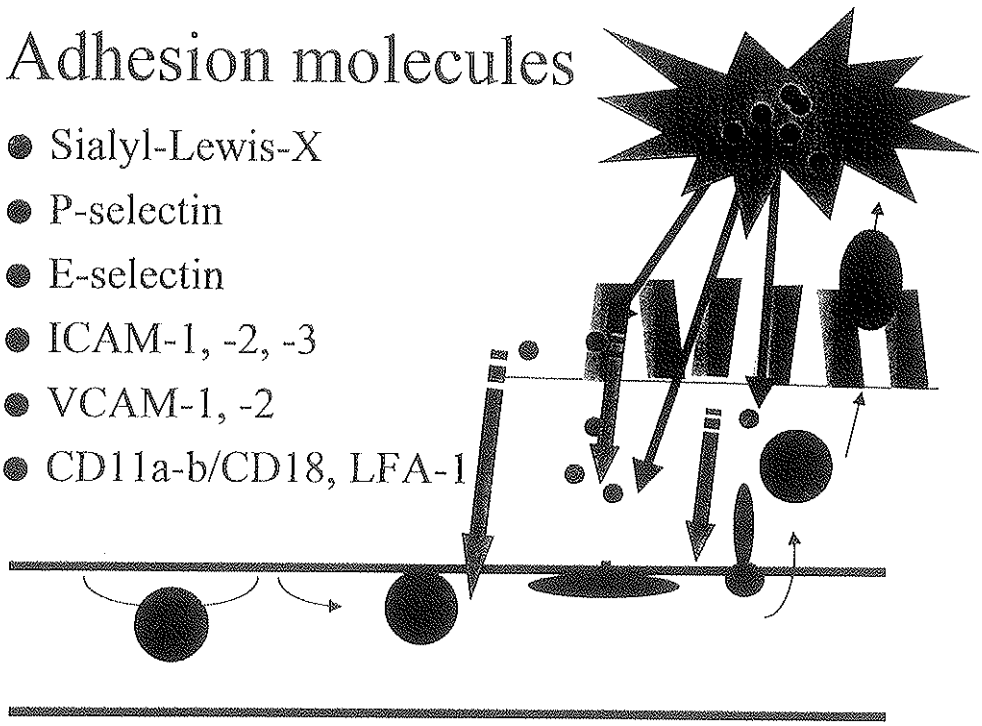
- Immunohistochemistry on biopsies

  IL-8 and GRO-α in the epithelium

Salvi *et al,* Am J RCCM, *in press*
Salvi *et al, submitted*

Adhesion molecules

- Sialyl-Lewis-X
- P-selectin
- E-selectin
- ICAM-1, -2, -3
- VCAM-1, -2
- CD11a-b/CD18, LFA-1



Diesel exhaust *300* $\mu g/m^3$ PM_{10}

	AIR (Median, IQR)	DIESEL (Median, IQR)	p-value
ICAM-1	48.9 (27.6-58.6)	93.2 (83.8-95.8)	<0.001
VCAM-1	0.6 (0.0-3.5)	2.2 (0.8-5.6)	<0.05
E-selectin	24.5 (16.0-33.3)	23.5 (10.6-35.0)	ns
P-selectin	25.0 (17.2-35.7)	30.7 (19.3-40.2)	ns

Salvi *et al,* Am J RCCM, in press

Diesel exhaust *300* $\mu g/m^3$ PM_{10}

	AIR (Median, IQR)	DIESEL (Median, IQR)	p-value
LFA-1+ cells			
- Epithelium	0.09 (0.0-2.7)	5.7 (3.0-22.4)	<0.005
- Submucosa	1.4 (0.0-16.6)	43.9 (10.3-76.9)	<0.05
VLA-4+ cells			
- Epithelium	0.0 (0.0-0.0)	0.0 (0.0-5.0)	ns
- Submucosa	0.6 (0.0-5.9)	5.7 (0.0-16.6)	0.0843

Salvi *et al,* Am J RCCM, in press 1998

Diesel exhaust *300* $\mu g/m^3$ PM_{10}

	AIR (Median, IQR)	DIESEL (Median, IQR)	p-value
Neutrophils			
- Epithelium	0.83 (0.0-2.5)	3.69 (1.81-6.71)	<0.05
- Submucosa	21.8 (17.7-35.3)	59.9 (32.4-90.9)	<0.005
Mast cells			
- Epithelium	0.0 (0.0- 0.44)	0.0 (0.0-0.0)	ns
- Submucosa	8.8 (7.7-14.9)	32.7 (14.7-46.2)	<0.005

Salvi *et al,* Am J RCCM, in press 1998

Diesel exhaust *300* $\mu g/m^3$ PM_{10}

	AIR (Median, IQR)	DIESEL (Median, IQR)	p-value
CD3+ cells			
- Epithelium	3.8 (0.0-13.7)	23.5 (9.9-31.9)	<0.05
- Submucosa	5.9 (1.2-18.5)	24.9 (9.3-59.9)	<0.05
CD4+ cells			
- Epithelium	0.3 (0.0-0.7)	2.9 (1.4-6.0)	<0.005
- Submucosa	3.2 (0.7-10.6)	13.1 (5.1-35.3)	<0.05
CD8+ cells			
- Epithelium	2.4 (0.0-5.5)	7.2 (2.9-20.4)	<0.05
- Submucosa	2.3 (0.2-15.5)	17.4 (2.9-37.1)	0.09

Salvi *et al,* Am J RCCM, in press

Diesel exhaust *300* $\mu g/m^3$ PM_{10}

- Bronchial wash and BAL
  - ↑ PMNs
  - ↑ CD19+
  - ↑ histamine
  - ↑ fibronectin
- Peripheral blood
  - ↑ Thrombocytosis

Salvi *et al,* Am J RCCM, *in press*
Salvi *et al*, *submitted*

Diesel exhaust exposure - induced sputum

- 300 $\mu g/m^3$ particles for 1 hour vs air
- 15 healthy non-atopic subjects
- Induced sputum 6 and 24 hours after exposure

↑ IL-6, IL-8, histamine and PMNs

Nordenhäll, *submitted*

Diesel exhaust *100* µg/m^3 PM_{10}

25 healthy subjects, two-hour exposure

- Immunohistochemistry on biopsies
  - ↑ P-Selectin, ICAM-1
- Bronchial wash and BAL
  - ↑ IL-6, IL-8, PMNs, lymphocytes
- *15 atopic asthmatics*

  Biopsies and lavages currently evaluated

Adhesion molecule expression in bronchial biopsies

	Air	Diesel exhaust	p-value
ICAM-1	63.6 (58.0-71.2)	66.4 (59.3-79.4)	ns
VCAM-1	4.8 (2.1-10.4)	8.8 (4.5-12.6)	<0.05
E-selectin	20.2 (11.3-27.2)	20.2 (15.1-30.4)	ns
P-selectin	52.4 (45.6-64.1)	66.7 (58.2-75.8)	<0.01

% of submucosal blood vessels stained positive with pan-endothelial antibody (EN4)

Data are given as Md and Q_1-Q_3

Cells in bronchial biopsies

	Air	Diesel exhaust	p-value
CD3+ lymphocytes			
epithelium	1.7 (0.4-3.1)	3.0 (1.5-6.1)	<0.05
submucosa	30.3 (21.1-87.0)	30.5 (18.5-74.6)	ns
Neutrophils submucosa	63.6 (58.0-71.2)	66.4 (59.3-79.4)	ns
Mast cells Submucosa	16.5 (11,6-16,5)	16,9 (12,3-16,8)	ns

Additional countings in epithelium and submucosa ns.

Data are given as Md and Q_1-Q_3

Bronchial wash and BAL

	Air	Diesel exhaust	p-value
BW			
IL-6 pg/ml	3.3 (1.8-5.4)	5.1 (1.8-9.2)	<0.05
IL-8 pg/ml	42 (28-58)	54 (30-75)	<0.05
neutrophils x10^4/ml	1.5 (0.7-2.2)	2.0 (1.1-3.1)	=0.069
neutrophils %	17.2 (11.2-22.1)	22.0 (16.6-30.1)	p<0.02
BAL			
lymphocytes x10^4/ml	1.5 (1.2-1.8)	2.0 (1.3-2.6)	p<0.05

Data are given as Md and Q_1-Q_3

Diesel exhaust *100* $\mu g/m^3$ PM_{10}

- The acute cytokine and chemokine presence, in terms of IL-6 and IL-8 in BW, together with enhanced expression of the vascular adhesion molecules P-selectin and VCAM-1 in the bronchial biopsies suggest an early recruitment of inflammatory cells.
- The reduction of CD3+ lymphocytes in the bronchial epithelium together with appearance of increased numbers in BAL, indicate ongoing lymphocyte migration into the air spaces.
- Mechanisms for neutrophil migration were present, though not fully developed at 6 hours after exposure.

Conclusion - DE*100* $\mu g/m^3$ PM_{10}

- Exposure to diesel exhaust containing PM 100 $\mu g/m^3$ induces inflammatory reactions in the airways of healthy subjects.
- The changes showed qualitative similarities, but were less pronounced than after 300 $\mu g/m^3$ (Salvi et al).
- The profile of the inflammatory markers suggests a slower development of airway inflammation after 100 μg PM $/m^3$ compared with 300 $\mu g/m^3$ (Salvi et al).
- A later time point of investigation, 12-18 hours after exposure, may have reflected a more established state of inflammation.

Diesel exhaust

- Pro-inflammatory effects on epithelium and immunoregulatory cells
- Pronounced inflammation in healthy subjects

  - data from asthmatics coming

- Mechanisms of possible importance in asthma, allergy and COPD

- Connections with Cardiovascular disease ?

Human Allergic Responses to Diesel Exhaust Particles

David Diaz-Sanchez
Division of Clinical Immunology and Allergy, University of California Los Angeles School of Medicine, Los Angeles, CA 90024-1680, U.S.A.

"Large numbers of the people have been transferred from the country ... to the town, and have thus been placed in circumstances where the predisposition to hay-fever would be most rapidly developed" This description of the growing epidemic of allergic disease and its clear association with urbanization was written in 1873 only fifty years after the first ever report of a case of hay fever. Since that time, many epidemiological and correlation studies have provided indirect evidence of an increased incidence of asthma and atopy linked to airborne pollution. The dramatic rise in expression of human allergic airway disease in the past two hundred years parallels the increase in fossil fuel combustion -- airway allergic disease was even called a disease of industrialization as early as 1907. Burning of fossil fuels generates a variety of xenobiotic compounds among which the polyaromatic hydrocarbons (PAH) and monofunctional inducers of oxidative stress (MIOS) are of particular interest. This type of pollution has increased 1000's of fold since the industrial revolution began.

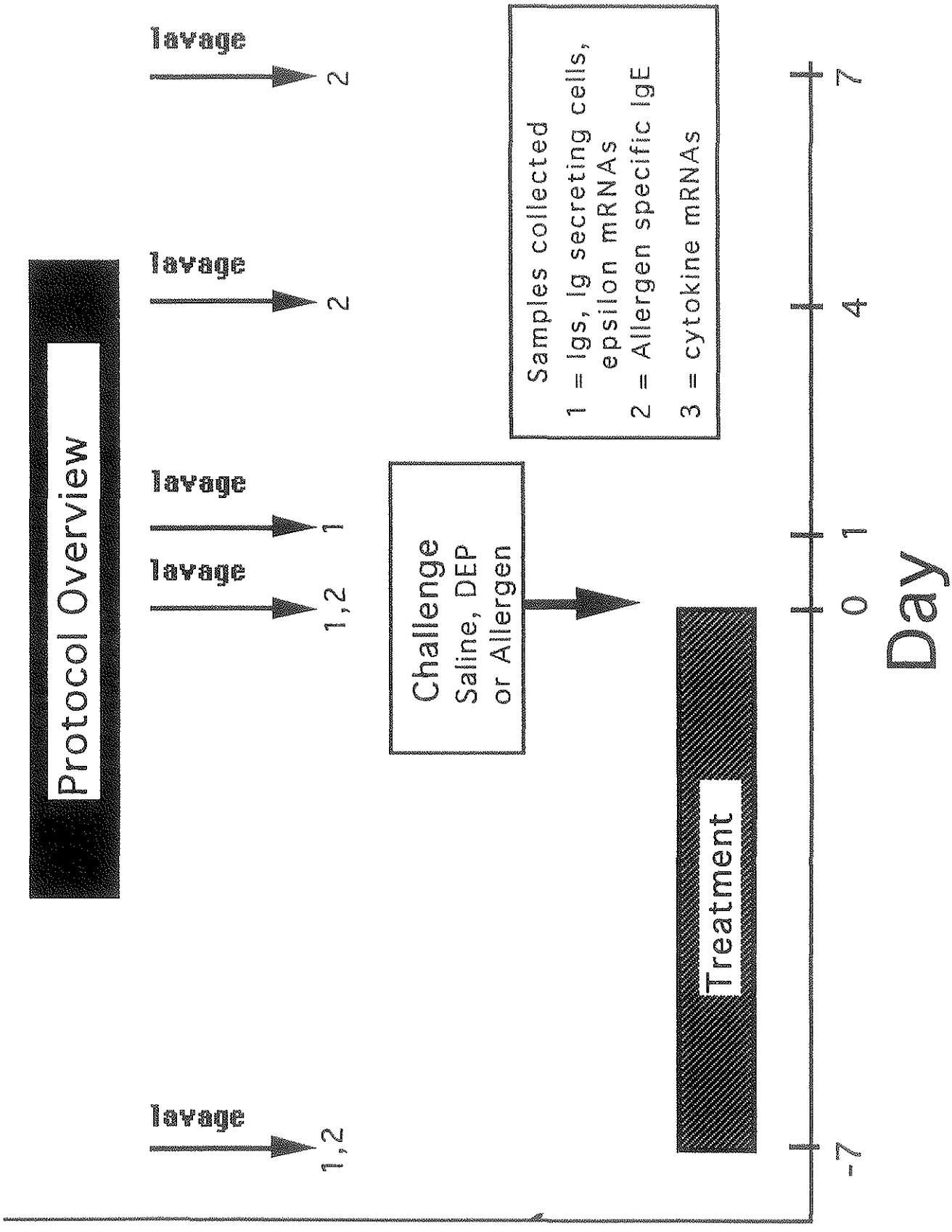
Allergic rhinitis (hay fever) is a common illness involving the nose, throat, and eyes. Often, persons with this allergic condition of their upper airway have allergic reactions in their lungs (asthma) as well. These reactions are caused by the presence of a particular protein called allergic antibodies (immunoglobulin E or IgE) which reacts to foreign allergy material (i.e. pollen). The severity of allergic symptoms normally correlates with the levels of these antibodies. Previous epidemiological studies have shown correlations between total air pollution, pulmonary function and allergic airway disease and have suggested that the pollutants act by non-specific mucosal inflammatory effects.

We have employed human systems to investigate the effects of Diesel Exhaust Particles (DEP) and the chemicals contained therein upon allergic inflammation as measured by IgE production. We initially demonstrated that DEP induced enhanced IgE production both *in vitro* and *in vivo*. We performed a series of *in vivo* experiments on human subjects. When the nasal passages of subjects were sprayed with 0.3 mg DEP there was a significant rise (generally 4-5 fold) in local production of IgE four days later. Combined challenge with pollen (ragweed) and DEP led to a marked

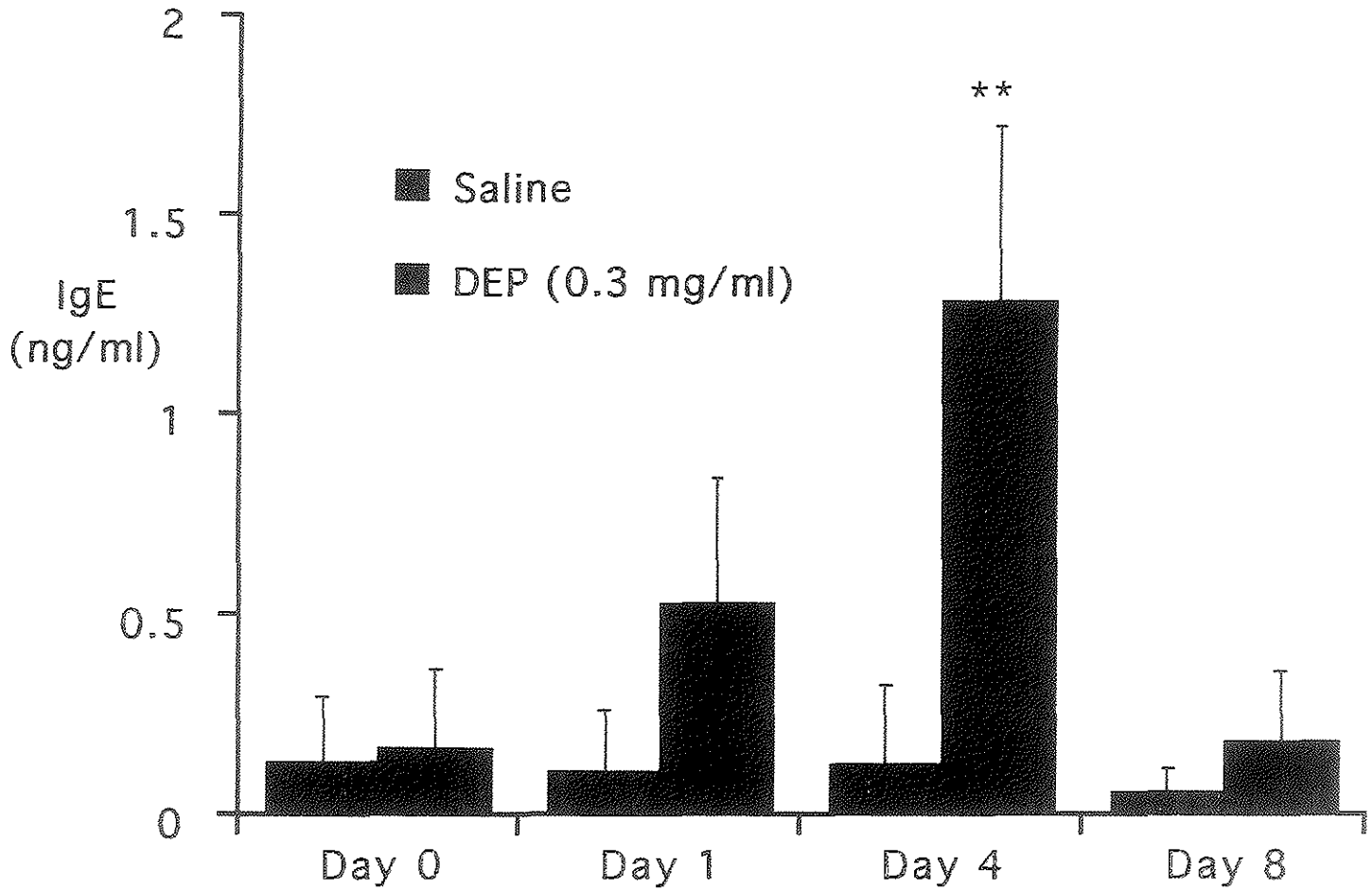
increase in local IgE production specific for ragweed and to the production of key proteins that promote IgE production that are made only by a certain subpopulation of immune cells (TH2 cells). DEP have recently been shown to directly bind allergens molecules and thereby provide a mechanism for natural co-administration. These results indicate that DEP can exacerbate pre-existing allergic responses.

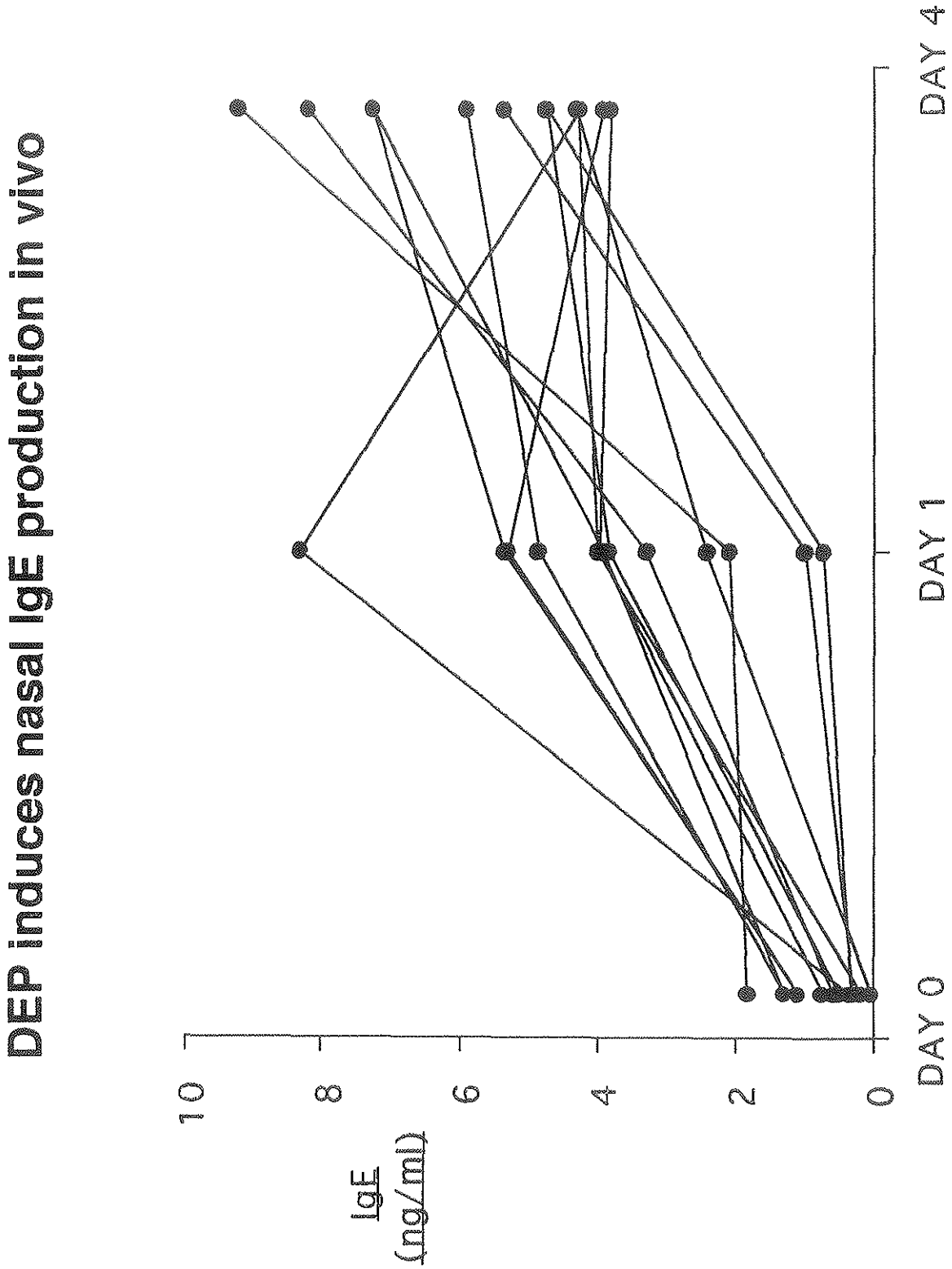
We next determined that DEP, could induce primary sensitization, that is make an individual allergic to a protein they had not encountered before (i.e. a neo-antigen). One such protein is Keyhole Limpet Hemocyanin (KLH); it is found in the blood of a certain mollusk which is inedible. When subjects were challenged with KLH they made no IgE, but when it was administered in the presence of DEP, IgE antibodies to KLH were detected. Thus, DEP may act as mucosal adjuvants to not only enhance but also initiate allergic responses to inhaled proteins or materials in humans.

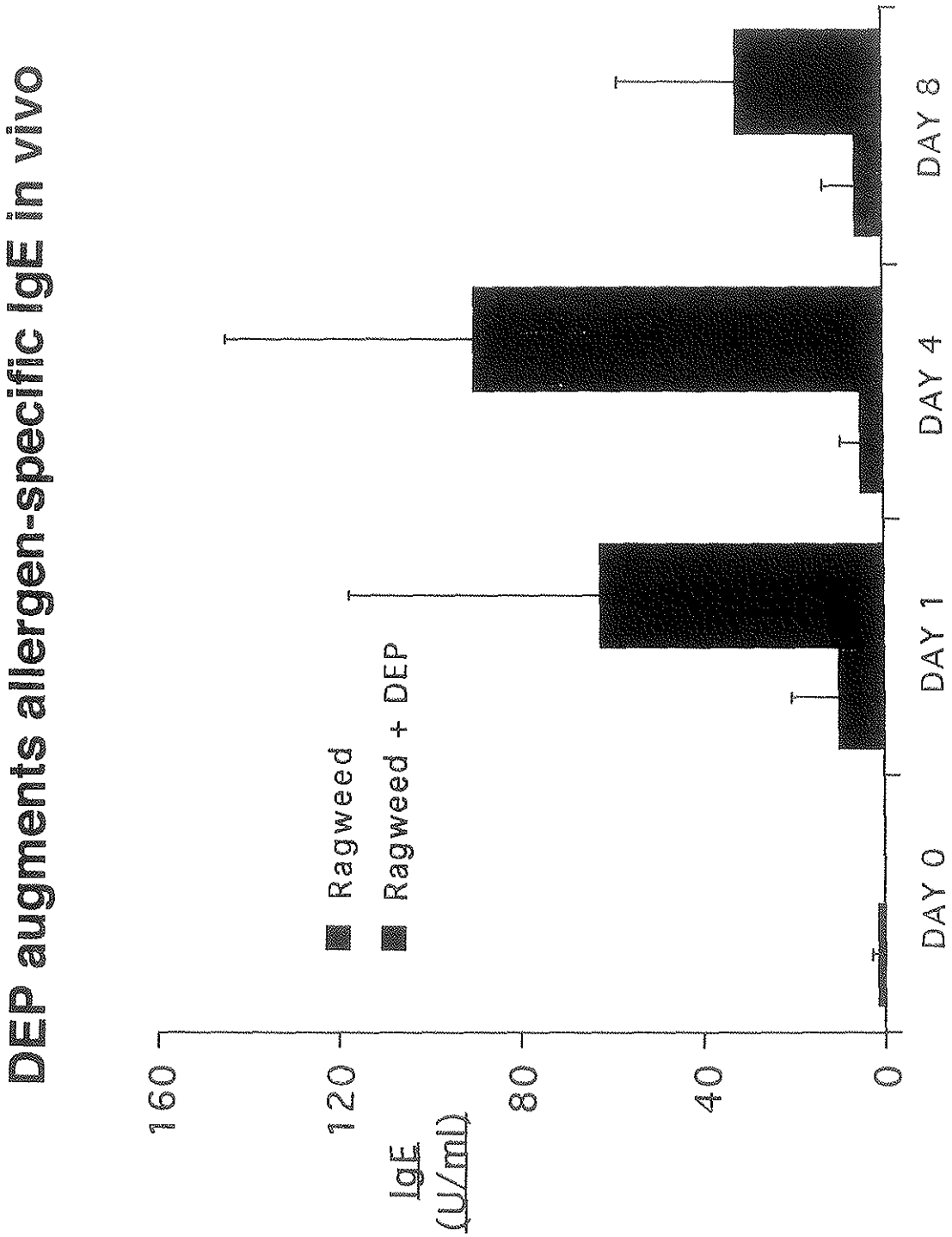
A key question in these studies is what are the pathways by which DEP drive allergic inflammation. Whether it is the particulate nature of DEP, the associated chemicals or both that account for the mechanism of action of DEP is still uncertain. However,, we have found that the organic extract of DEP can enhance IgE production from B cells *in vitro,* as can phenanthrene, the major polyaromatic hydrocarbon found in DEP. Additionally, following challenge of allergic subjects with phenanthrene an increase in IgE is observed but little or no inflammation as characterized by cell influx. Obversely, when subjects are sprayed intranasally with carbon particles lacking the chemicals, a large influx of cells in the nasal mucosa was detected but no increase in IgE was apparent. These results suggest that while the particles themselves cause local inflammation and may act as an irritant, it is the chemicals that act on the immune system to promote an allergic antibody response. These data establish important activation pathways for PAH in the human immune system and provide potential molecular targets to modulate the effect of environmental pollutants on allergic inflammation.

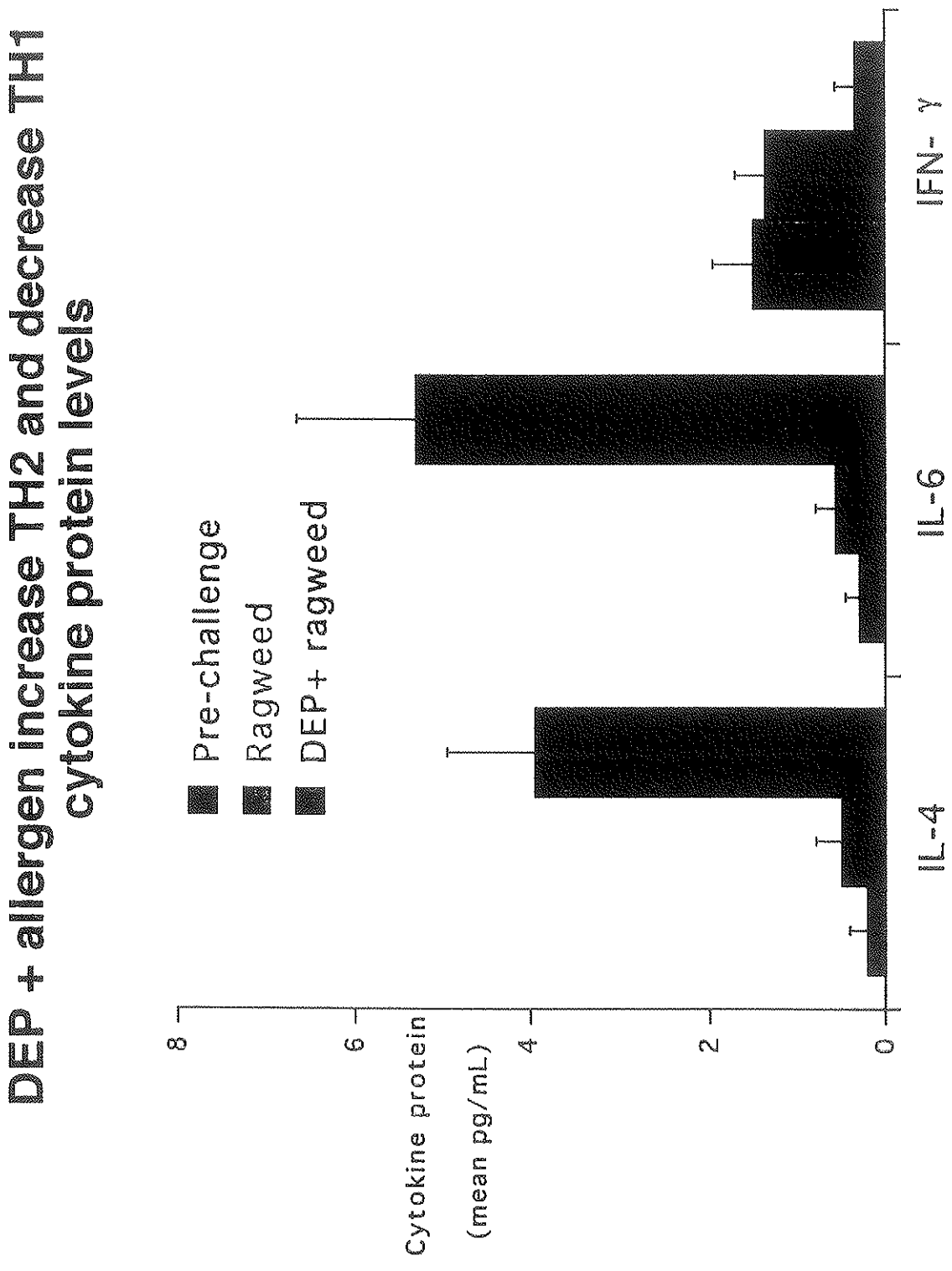

Protocol Overview
lavage
2
lavage
2
lavage
1
lavage
1,2
lavage
1,2
Challenge
Saline, DEP
or Allergen
Samples collected
1 = Igs, Ig secreting cells,
epsilon mRNAs
2 = Allergen specific IgE
3 = cytokine mRNAs
Treatment
-7
0
1
4
7
Day

Diesel Exhaust Particles increase nasal IgE production

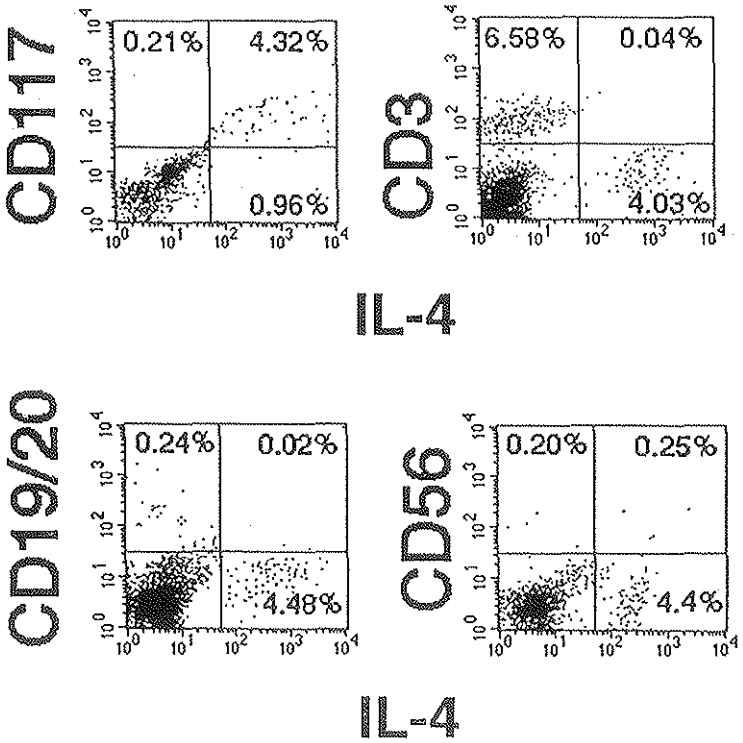


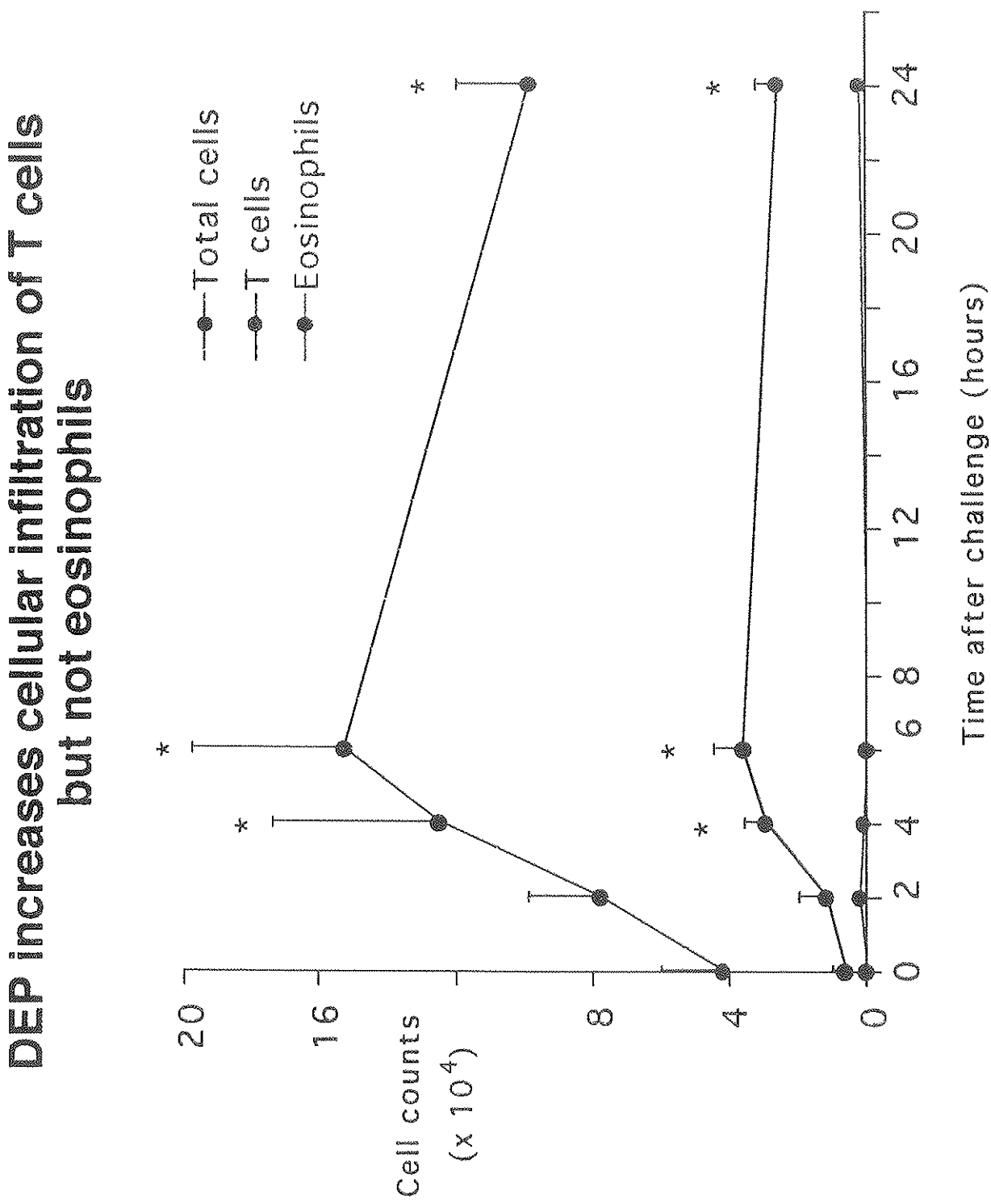

DEP induces nasal IgE production in vivo
IgE (ng/ml)
10
8
6
4
2
0
DAY 0
DAY 1
DAY 4

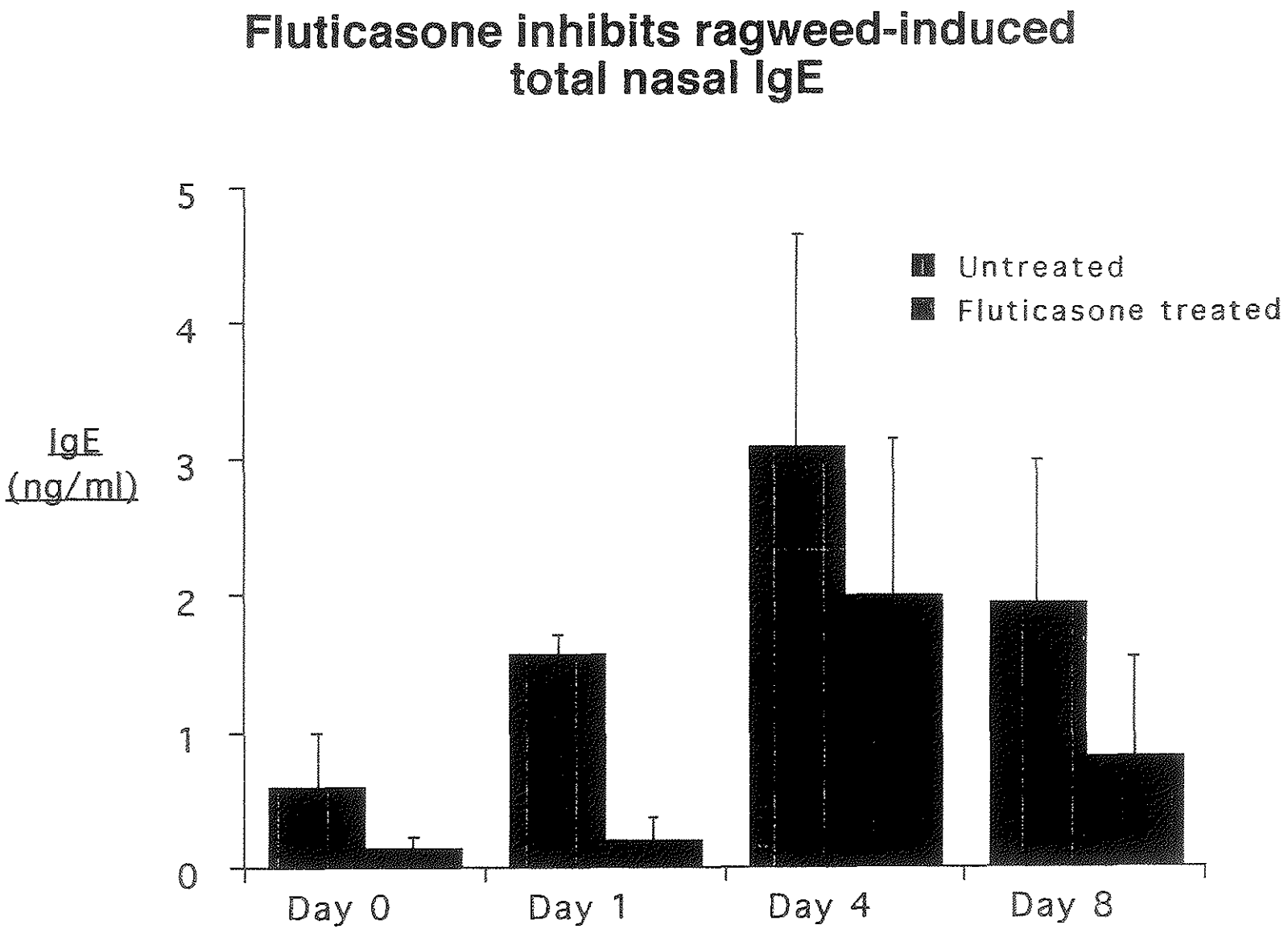

DEP augments allergen-specific IgE in vivo
IgE (U/ml)
160
120
80
40
0
Ragweed
Ragweed + DEP
DAY 0
DAY 1
DAY 4
DAY 8

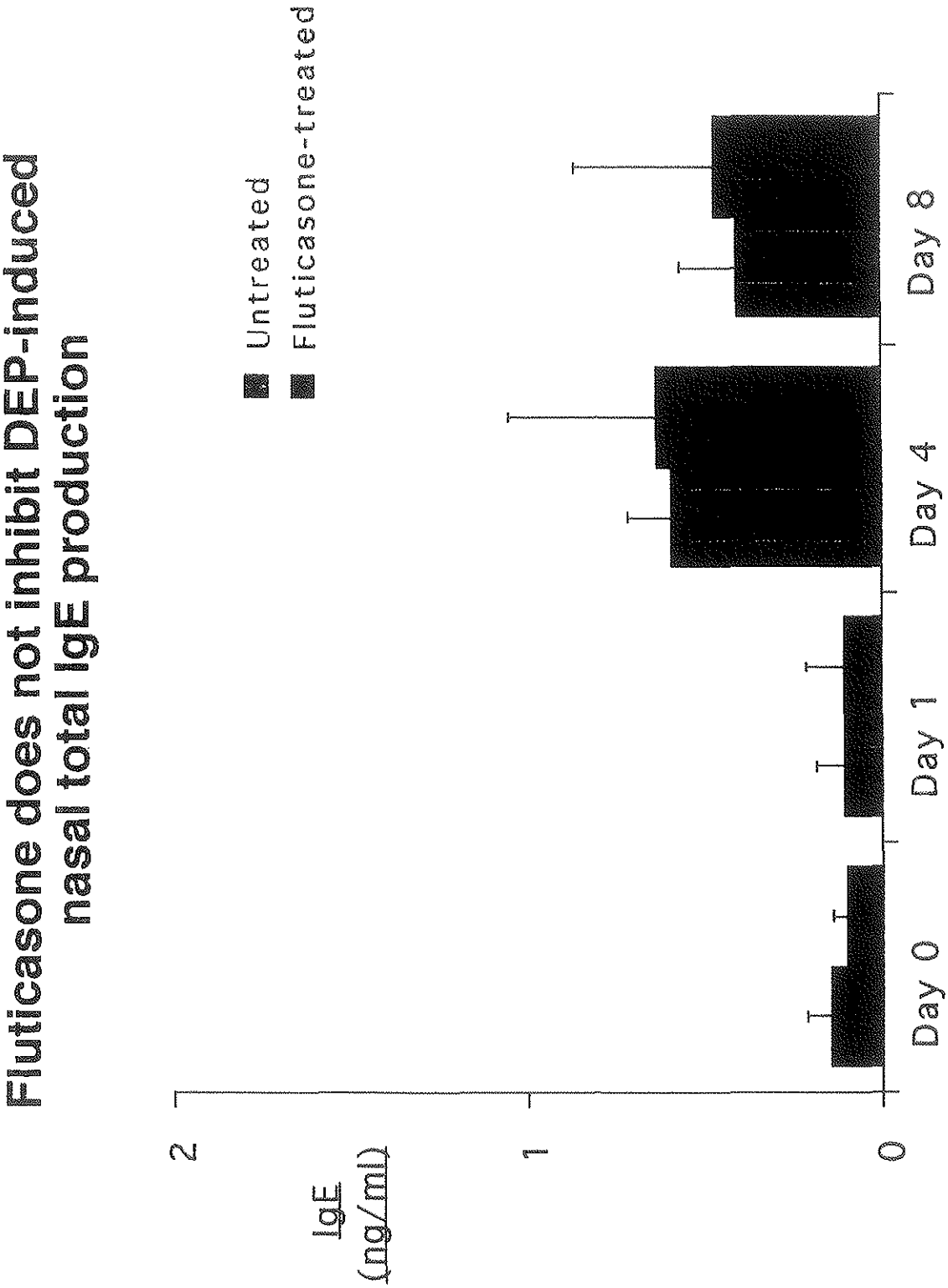

DEP + allergen increase TH2 and decrease TH1 cytokine protein levels
Pre-challenge
Ragweed
DEP+ ragweed
Cytokine protein (mean pg/mL)
8
6
4
2
0
IL-4
IL-6
IFN- γ

Human Nasal Cells Containing IL-4 Four Hours After DEP Challenge are C-Kit (CD117) Positive.

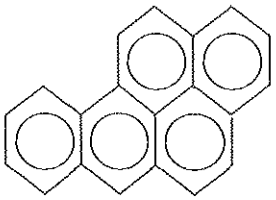



DEP increases cellular infiltration of T cells but not eosinophils
Total cells
T cells
Eosinophils
Cell counts (x 10^4)
20
16
8
4
0
0
2
4
6
8
12
16
20
24
Time after challenge (hours)
*

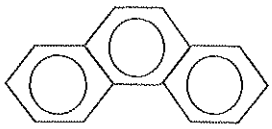

Fluticasone inhibits ragweed-induced total nasal IgE
IgE (ng/ml)
5
4
3
2
1
0
Untreated
Fluticasone treated
Day 0
Day 1
Day 4
Day 8


Fluticasone does not inhibit DEP-induced nasal total IgE production
Untreated
Fluticasone-treated
IgE (ng/ml)
2
1
0
Day 0
Day 1
Day 4
Day 8

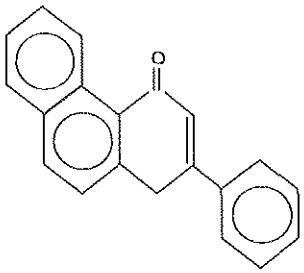
Polyaromatic hydrocarbons and other chemicals of interest



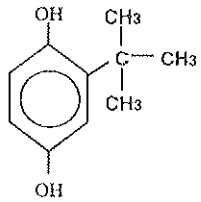
Benzo(a)pyrene



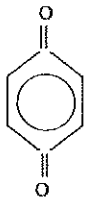
Phenanthrene



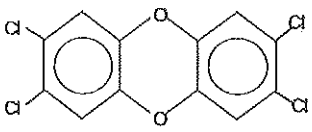
β-Naphthoflavone



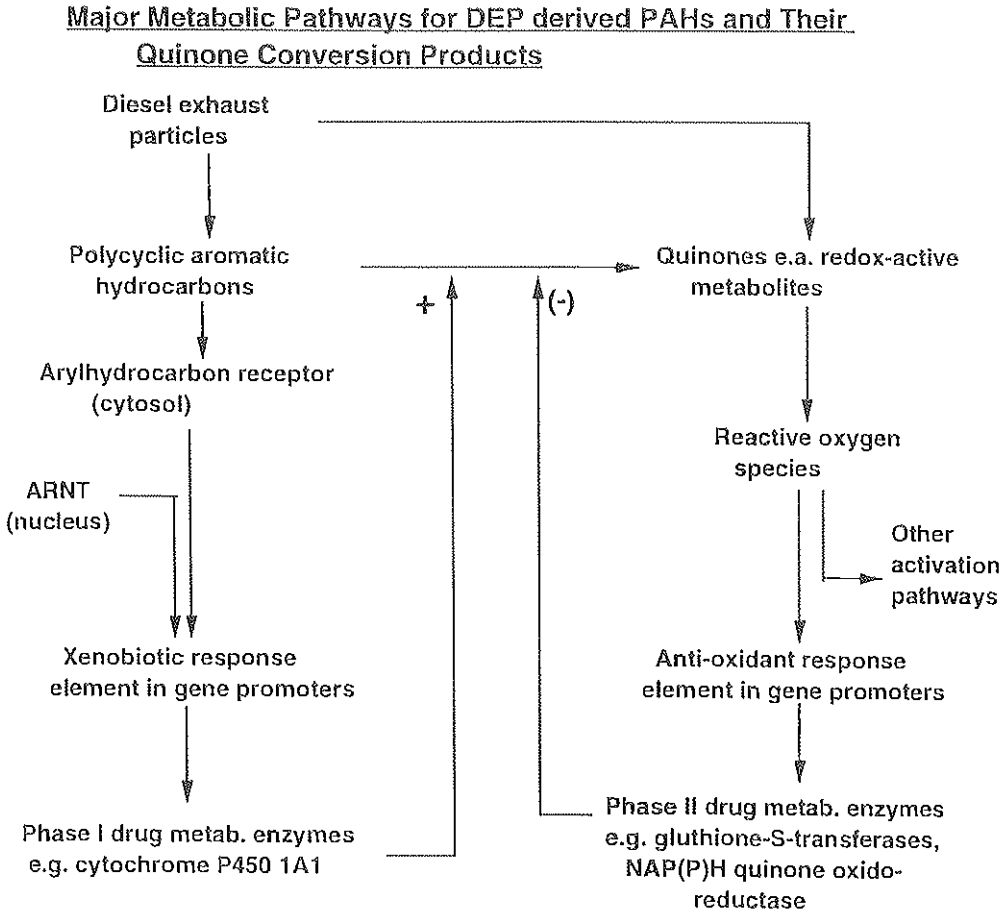
Tert-butylhydroxy-quinone



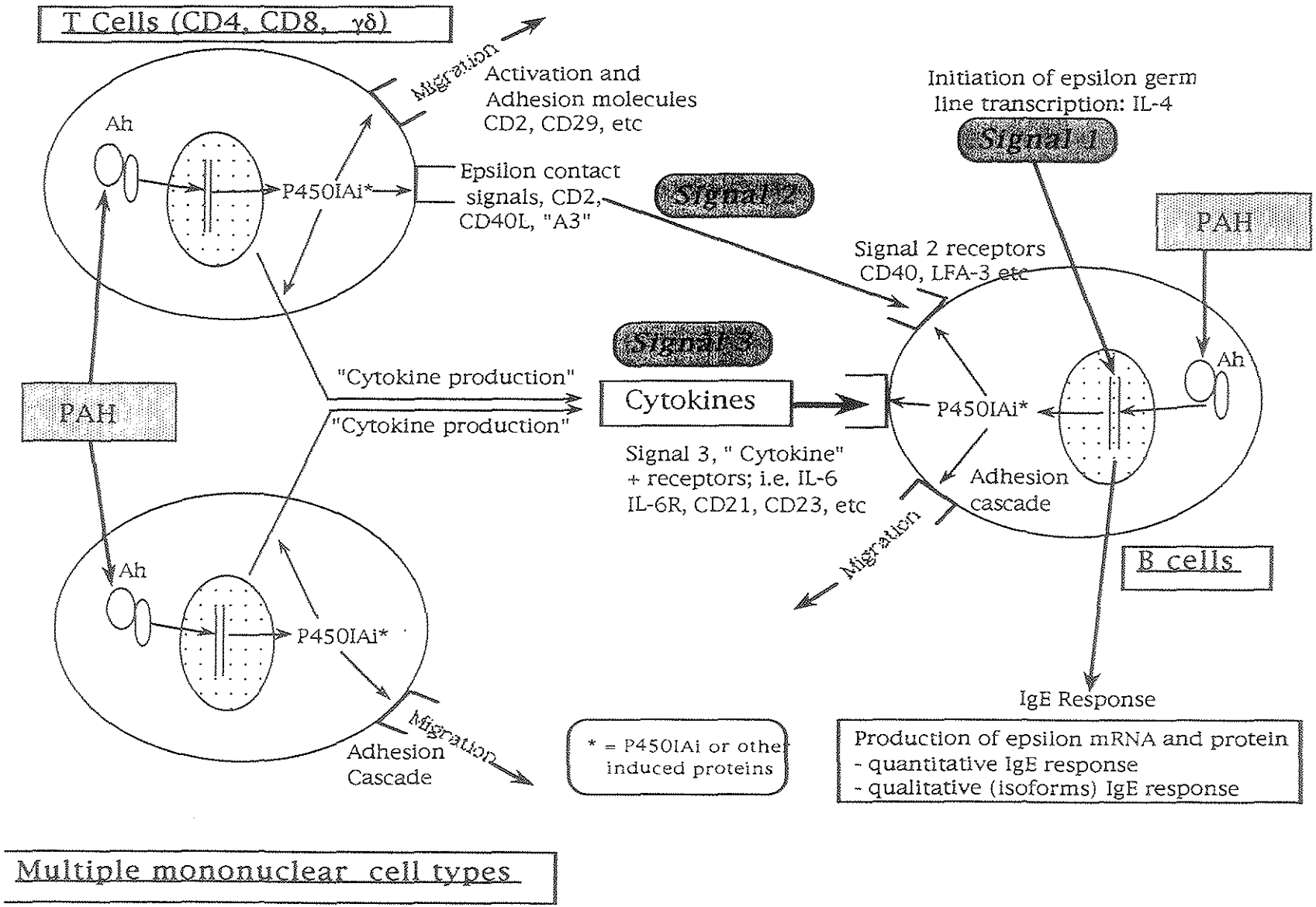
Quinone



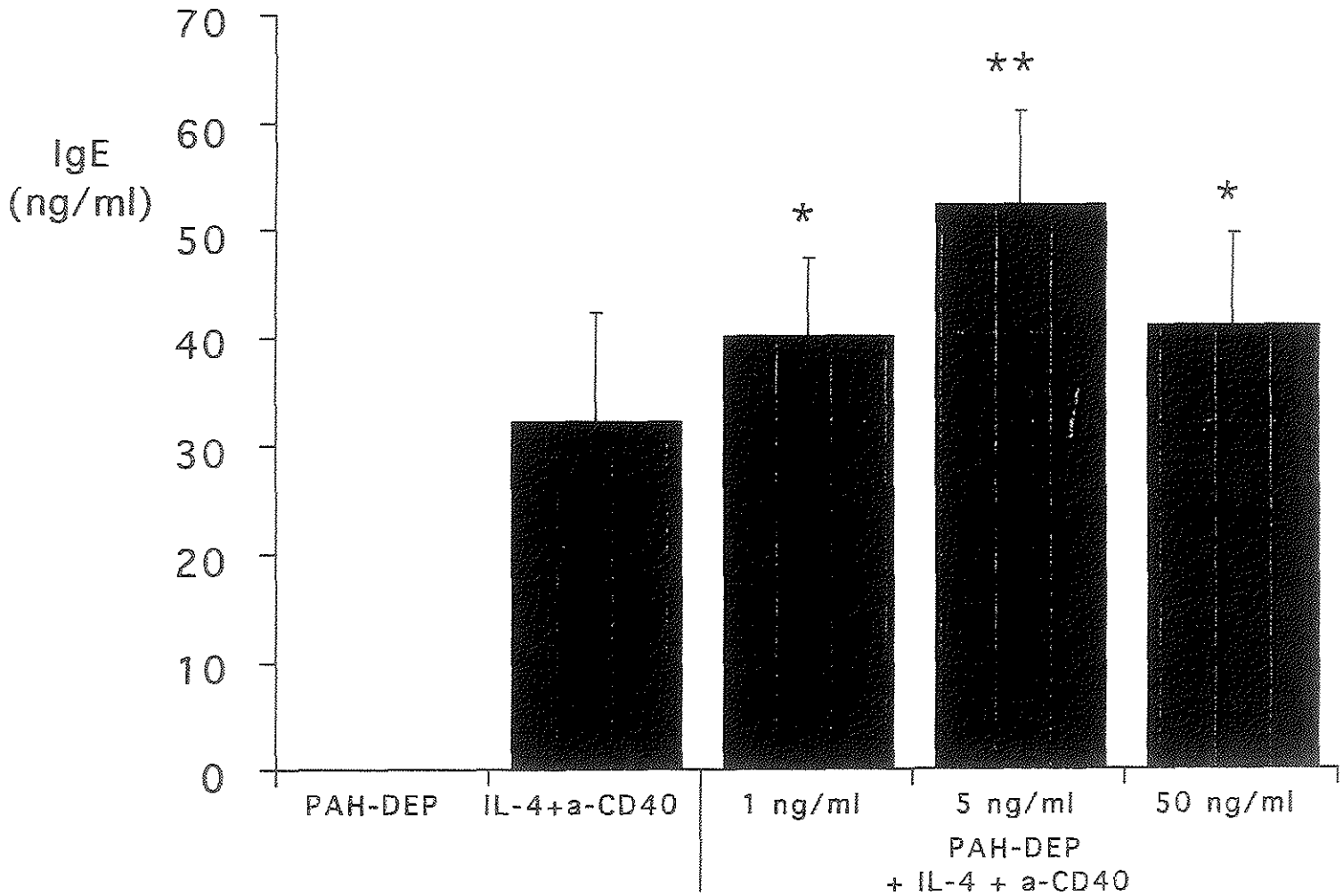
2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)


Major Metabolic Pathways for DEP derived PAHs and Their Quinone Conversion Products
Diesel exhaust particles
Polycyclic aromatic hydrocarbons
Quinones e.a. redox-active metabolites
+
(-)
Arylhydrocarbon receptor (cytosol)
Reactive oxygen species
ARNT (nucleus)
Other activation pathways
Xenobiotic response element in gene promoters
Anti-oxidant response element in gene promoters
Phase I drug metab. enzymes e.g. cytochrome P450 1A1
Phase II drug metab. enzymes e.g. gluthione-S-transferases, NAP(P)H quinone oxido-reductase

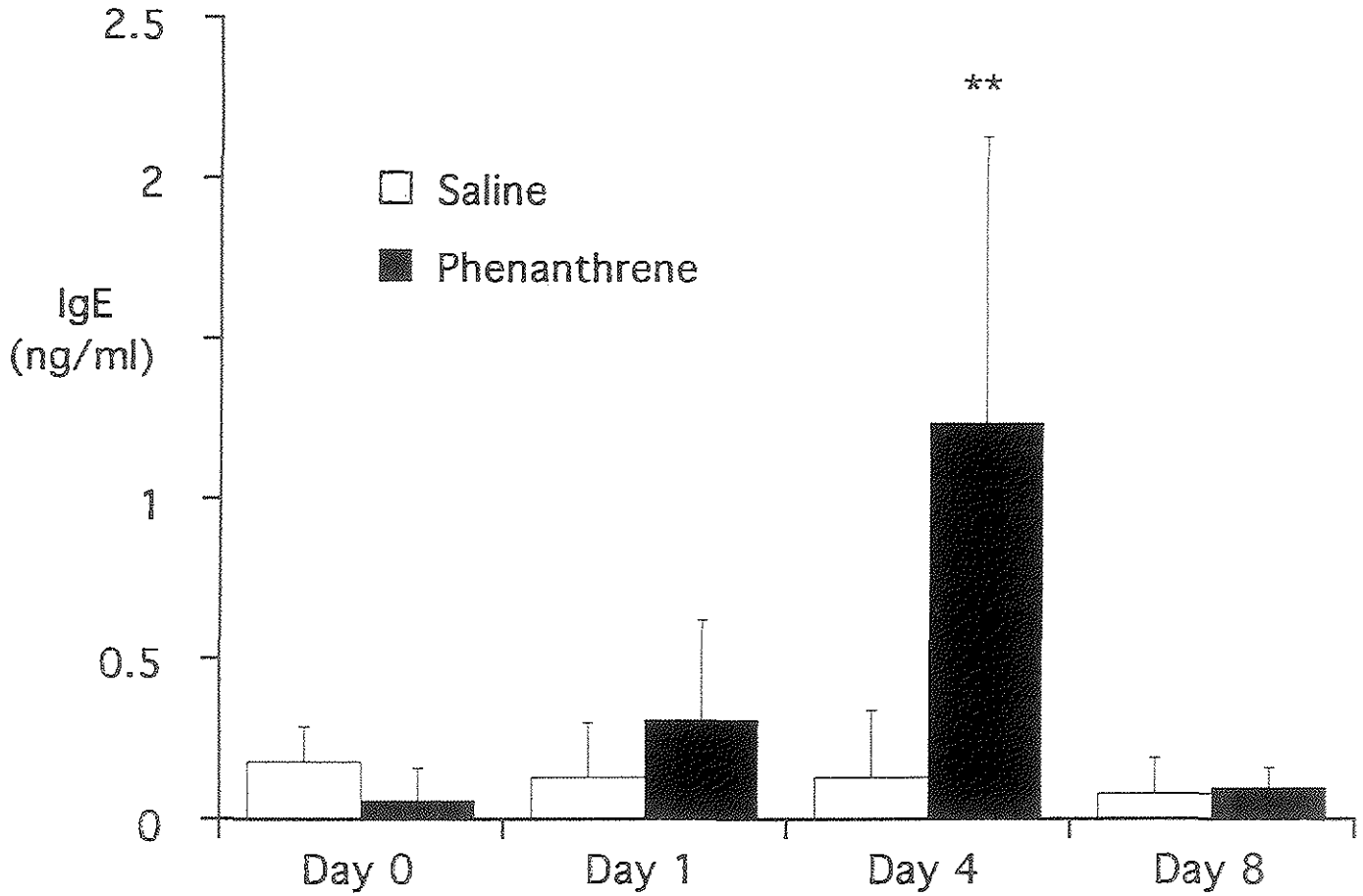
IgE response pathways and possible PAH interactions



Polyaromatic hydrocarbons from diesel exhaust particles will enhance IgE production in vitro



Intranasal Challenge with Phenanthrene Induces Local IgE Production



Effects of DEP on Human *in vivo* Allergic Responses

Diesel Exhaust Particles

- Enhance Local Mucosal IgE Production
- Induce an Inflammatory Response of Cells, Chemokines and Cytokines
- PAH Enhance Local Mucosal IgE Production Without a Measurable Cellular Inflammatory response

Diesel Exhaust Particles Plus Allergen

- Enhance Local Antigen Specific IgE Production
- Deviate Cytokine Production Toward a Th2 Profile
- Drive In Vivo Isotype Switch to IgE

Diesel Exhaust Particles Plus Neoantigen

- Synergize to Drive Primary Sensitization to the Antigen

APPENDICES

HEI Profile

Workshop Participants

HEI PROFILE

WHAT IS HEI?

The Health Effects Institute (HEI) is a public–private partnership established in 1980 to provide decision makers, scientists, and the public with high-quality, impartial, and relevant scientific information about the health effects of air pollution and other environmental contaminants. The intent of HEI has been to develop the facts concerning health effects carefully and credibly so that controversy about the facts themselves will be removed from the adversarial agenda and the debates over clean air can instead focus on national and international policy issues.

HEI is an unusual model of government-industry collaboration in support of research. The Institute has historically received half of its core funds from the U.S. Environmental Protection Agency and half from worldwide manufacturers States. HEI also receives funding from other organizations to supplement funding for specific projects. For example, the European Chemical Industry Council (CEFIC) and its U.S. counterpart, the Chemical Manufacturers Association, are contributing to 1,3-butadiene biomarker studies, and the California Air Resources Board and the Engine Manufacturers Association are contributing to new diesel epidemiology studies.

The Institute regularly consults with its sponsors and others to help focus its research priorities. None of the contributors has control over the selection, conduct, or management of HEI studies, however, and HEI makes no recommendations on how to apply research to regulatory policy.

The Institute's autonomy is supported, even beyond the statements in its charter, by the integrity and commitment of both its scientific leadership and its Board of Directors. In addition, HEI staff work hand in hand with two external and independent committees for research and review, each consisting of distinguished scientists knowledgeable about the scientific issues inherent to investigating the health effects of air pollution.

HOW DOES HEI WORK?

Research Selection and Management

After seeking advice from HEI's sponsors and others interested in its work, the HEI Research Committee determines the research priorities of the Institute and solicits applications from the scientific community. Applications are reviewed first for scientific quality by an ad hoc panel of appropriate experts, and are then reviewed by the HEI Research Committee for both quality and relevance to the goals of the research program. Applications ultimately undergo final approval by the Board of Directors, which also reviews the procedures, independence, and quality of the selection process.

During the course of each study, the Research Committee and scientific staff maintain close contact with HEI-funded investigators by means of progress reports, site visits, workshops, and the HEI Annual Conference. At the annual conference, HEI investigators, Research Committee and Review Committee members, HEI staff, representatives of sponsor organizations, invited guests, and other participants meet to share information and develop new ties to strengthen the HEI community of scholars.

Independent Review Process

In order to fulfill its mission of providing timely, high-quality research results for decision makers, HEI has developed a rigorous review process to evaluate results of the research it funds. A separate HEI Review Committee, which has no role in the review of applications or in the selection of projects, assesses the scientific quality of each completed study and evaluates its contribution to unresolved scientific questions. The investigator's final report, extensive summary data, and a commentary by the Review Committee are published together by HEI.

THE HEI RESEARCH PROGRAM

Since its inception, the HEI research program has addressed important questions about the health effects of a variety of pollutants, including carbon monoxide, methanol, diesel exhaust particles, nitrogen oxides, and ozone. The current research program focuses on air toxics, ambient particles, and oxygenates and metals emitted from fuels added to gasoline. As part of the assessment of these pollutants, HEI has funded studies to increase our understanding of the mechanisms of diseases, to develop better methods of assessing health effects, to determine exposure and dose, and to address issues common to many pollutants.

The program has included theoretical, in vitro, animal, controlled human exposure, and

epidemiology studies. The choices of which pollutants to study or scientific questions to investigate have been based on many considerations, including evaluation of issues raised by sponsors, analysis of regulatory needs, and uncertainties about health effects of specific pollutants. HEI has, on some occasions, produced special reports to evaluate the state of existing science in areas related to policy and to determine research needs in new areas. HEI has also conducted or participated in special workshops on the health effects of specific pollutants such as fine particles, the subject of this Communication.

To guide its research efforts, HEI produces and regularly updates a *Strategic Plan for the Health Effects of Air Pollution*. In 2000–2004, the Strategic Plan will focus on key areas that are broadly relevant in the United States, Europe, and Asia. These include understanding the air pollution mixture (particulates, gaseous pollutants, and toxics), assessing the health effects of emerging technologies and fuels, and measuring the health results of environmental regulation.

WORKSHOP PARTICIPANTS

Nancy Adams
Quality Assurance
US Environmental Protection Agency
Alexander Drive
Research Triangle Park, NC 27711
tel: (919) 541- 5510
fax: (919) 541-0496
email: *adams.n@usepa.epa.gov*

Saunders Aldridge
Hunter, Maclean, Exley, & Dunn, P.C.
P.O. Box 9848
Savannah, GA 31412
tel: (912) 236-0261
fax: (912) 236-4936
email: *saldridge@hmed.com*

Robert Anderson
Rupprecht & Patashnick Co., Inc.
25 Corporate Circle
Albany, NY 12203
tel: (518) 452-0065
fax: (518) 452-0067
email: *randerson@rpco.com*

Michael Attfield
National Institute for Occupational Safety and Health (NIOSH)
1095 Willowdale Road
Morgantown, WV 26505
tel: (304) 285-5737
fax: (304) 285-5820
email: *mda1@cdc.gov*

Herman Autrup
Department of Environmental & Occupational Medicine
University of Aarhus
Vennelyst Boulevard 6
C-8000 Aarhus
Denmark
tel: + 45 8942 6180
fax: + 45 8942 6199
email: *ha@mil.au.dk*

John C. Bailar, III
Department of Health Studies
The University of Chicago
5841 South Maryland Avenue, MC 2007
Chicago, IL 60637
tel: (773) 834-1242
fax: (773) 702-1979
email: *jcbailar@midway.uchicago.edu*

Brent K. Bailey
Coordinating Research Council, Inc.
219 Perimeter Center Parkway, Suite 400
Atlanta, GA 30346
tel: (770) 396-3400
fax: (770) 396-3404
email: *bkbailey@crcao.com*

Brenda Barry
Environmental Health & Engineering
60 Wells Avenue
Newton, MA 02459
tel: (617) 964-8550
fax: (617) 964-8556
email: *bbarry@eheinc.com*

Nick Barsic
John Deere & Co.
P.O. Box 8000
Waterloo, IA 50704
tel: (319) 292-8152
fax: (319) 292-8457
emai: *barsicnicholasj@jdcorp.deere.com*

Rich Bechtold
QSS Group, Inc.
4500 Forbes Boulevard
Lanham, MD 20706
tel: (301) 429-2594
fax: (301) 918-4817
email: *richard.bechtold@qssgroupinc.com*

Tim Belian
Coordinating Research Council, Inc.
219 Perimeter Center Parkway, Suite 400
Atlanta, GA 30346
tel: (770) 396-3400
fax: (770) 396-3404
email: *tbelian@crcao.com*

Wolfgang Berg
Test Tracks and Emissions-Labs
DaimlerChrysler AG
HPC S402
D-70546 Stuttgart
Germany
tel: + 49 71 1175 5618
fax: + 49 71 1175 3141
email: *wolfgang.berg@daimlerchrysler.com*

Paolo Boffetta
Unit of Environmental Cancer Epidemiology
International Agency for Research on Cancer
150 Cours Albert-Thomas
69372 Lyon cedex 08
France
tel: + 33 4 7273 8485
fax: + 33 4 7273 8575
email: *boffetta@iarc.fr*

Jonathan Borak
234 Church St, Suite 1100
New Haven, CT 06510
tel: (203) 777-6611
fax: (203) 777-1411

Fred Brear
Performance, Emissions, and Combustion
Perkins Engines Co. Ltd.
Peterborough, Cambridgeshire PE1 5NA
U.K.
tel: + 44 1733 583213
fax: + 44 1733 582323
email: *fbrear@perkins-engines.com*

Pamela Brodowicz
Scientific Assessment Group of Assessment and Modeling Division
US Environmental Protection Agency
2000 Traverwood Drive
Ann Arbor, MI 48105
tel: (734) 214-4364
fax: (734) 214-4939
email: *brodowicz.pamela@epa.gov*

Patricia Brower
National Institute for Occupational Health and Safety (NIOSH)
1095 Willowdale Road
Morgantown, WV 26505
tel: (304) 285-5874
fax: (304) 285-5820
email: *plsi@cdc.gov*

Bert Brunekreef
Department of Environmental Sciences
Wageningen University and Research Center
P. O. Box 238
6700 AE Wageningen
The Netherlands
tel: + 31 317 -482080
fax: + 31 317 485278
email: *Bert.Brunekreef@staff.eoh.wau.nl*

William B. Bunn
Health Safety and Productivity
Navistar International Transportation Corporation
455 North City Front Plaza Drive
Chicago, IL 60611
tel: (312) 836-2301
fax: (312) 836-3959
email: *bunnwb@aol.com*

Kajsa Carr
EHLS-Toxicology
Centers for Disease Control
4770 Buford Hwy
Atlanta, GA 30341
tel: 770-488-7931
email: *kic9@cdc.gov*

Glen Cass
Environmental Engineering Science Department
California Institute of Technology
W. M. Keck Laboratories
1200 E. California Blvd.
Mail Code 138-78
Pasadena, CA 91125
tel: (626) 395-6888
fax: (626) 395-2940
email: *glen@eql.caltech.edu*

Steve Castleberry
Regnlatory Affairs
Mississippi Lime Company
7 Alby Street
P.O. Box 2247
Alton, IL 62002
tel: (618) 465-7741 ext 3406
fax: (618) 465-9218

John Cherrie
University of Aberdeen &
Institute of Occupational Medicine
8 Roxburgh Place
Edinburgh EH8 9SU
UK
tel: + 46 131 667 -5131
fax: + 46 131 667 0136
email: *jcherrie@iomhg.org.uk*

Michele Chevrier
Depollution Air Quality
Renault SA
64120 TCR Lab 250
1 Avenue du Golf
Guyancourt
France
tel: + 33 1 34 95 04 97
fax: + 33 1 34 95 05 01

Nigel Clark
Department of Mechanical and Aerospace Engineering
College of Engineering and Mineral Resources
West Virginia University
P. O. Box 6106
Morgantown, WV 26506-6106
tel: (304) 293-3111 ext 2311
fax: (304) 293-2582
email: *nclark@wvu.edu*

Russ Clayton
Environmental Monitoring and Engineering
ARCADIS Geraghty & Miller
6865 Prospectus Drive
Durham, NC 27713
tel: (919) 544-4535
fax: (919) 544-5690
email: *rclayton@gmgw.com*

Aaron Cohen
Health Effects Institute
955 Massachusetts Avenue
Cambridge, MA 02139
tel: (617) 876-6700
fax: (617) 876-6709
email: *acohen@healtheffects.org*

Maria Costantini
Health Effects Institute
955 Massachusetts Avenue
Cambridge, MA 02139
tel: (617) 876-6700
fax: (617) 876-6709
email: *mcostantini@healtheffects.org*

Dirk Dahmann
Institute for Research on Hazardous Substances
Waldring 97
D-44789 Bochum
Germany
tel: + 49 234 306 412
fax: + 49 234 306 353
email: *dahmann@igf.bergbau_bg.de*

Stanley Dawson
Office of Environmental Health Hazards Assessment (OEHHA)
California Environmental Protection Agency
1515 Clay Street, 16th Floor
Oakland, CA 94612
tel: (510) 622-3147
fax: (510) 622-3210
email: *sdawson@berkeley.cahwnet.gov*

David Diaz-Sanchez
Department of Clinical Immunology and Allergy
School of Medicine
University of California at Los Angeles
10833 Le Conte Avenue, 52-175 CHS
Los Angeles, CA 90095-1680
tel: (310) 825-9376
fax: (310) 206-8107
email: *ddiazsa@ucla.edu*

Mustafa Dosemeci
Occupational Epidemiology Branch
National Cancer Institute
6120 Executive Boulevard
Bldg. EPS, Room 8002
Rockville, MD 20892-7368
tel: (301) 435-4715
fax: (301) 402-1819
email: *dosemecim@mail.nih.gov*

John W. Duerr
Engineering Department
Detroit Diesel Corporation
13400 West Outer Drive
Detroit, MI 48239
tel: (313) 592 -7090
fax: (313) 592-5906
email: *jduerr01@detroitdiesel.com*

Susan Field
Senior Regulatory Engineer
Environmental Engineering
Toyota Technical Center, U.S.A., Inc.
1588 Woodridge, RR #7
Ann Arbor, MI 48105
tel: (734) 995-2086
fax: (734) 995-5971
email: *field@ttc-usa.com*

Murray Finkelstein
Occupational Health
McMaster University
400 University Avenue, 7th Floor
Toronto, Ontario M7A 1T7
Canada
tel: (416) 326 7879
fax: (416) 326 7889
email: *murray.finkelstein@utoronto.ca*

Tim French
Engine Manufacturers Association
Neal, Gerber & Eisenberg
2 N. LaSalle Street, Suite 2200
Chicago, IL 60602
tel: (312) 269-5670
fax: (312) 267-1747
email: *tfrench@ngelaw.com*

Jonathan Frisch
Health and Environmental Sciences
American Petroleum Institute
1220 L Street, NW
Washington, DC 20005
tel: (202) 682-8480
fax: (202) 682-8270
email: *Frischj@api.org*

Eric Fujita
Energy and Environmental Engineering Center
Desert Research Institute
2215 Reggio Parkway
P.O. Box 60220
Reno, NV 89512
tel: (775) 677-3311
fax: (775) 677-3157
email: *ericf@dri.edu*

John Gamble
Epidemiology Department
Exxon Biomedical Sciences
CN-2350 Mettlers Road
East Millstone, NJ 08875
tel: (732) 873-6004
fax: (732) 873-6009
email: *jfgambl@fpe.erenj.com*

Mahe Gangal
Canmet Department
Natural Resources Canada
555 Booth Street
Ottawa, Ontario K1A 0G1
Canada
tel: (613) 996-6103
fax: (613) 996-2597
email: *mgangal@nrcan.gc.ca*

Howard Garsh
Health Effects Institute
955 Massachusetts Avenue
Cambridge, MA 02139
tel: (617) 876-6700
fax: (617) 876-6709
email: *hgarsh@healtheffects.org*

Eric Garshick
Department of Medicine
Veterans Administration Medical Center
1400 VFW Parkway
West Roxbury, MA 02132
tel: (617) 323-7700 ext 5536
fax: (617) 363-5670
email: *egarshick@maverick.org*

Alan Gertler
Energy and Environmental Engineering Center
Desert Research Institute
2215 Reggio Parkway
P.O. Box 60220
Reno, NV 89512
tel: (775) 677-3142
fax: (775) 677-3303
email: *alang@dri.edu*

Alison Geyh
Health Effects Institute
955 Massachusetts Avenue
Cambridge, MA 02139
tel: (617) 876-6700
fax: (617) 876-6709
email: *ageyh@healtheffects.org*

Richard Gibbs
Bureau of Mobile Sources
Division of Air Resources
New York State Department of Environmental Conservation
50 Wolf Road
Albany, NY 12233-3255
tel: (518) 485-8913
fax: (518) 457-8831
email: *regibbs@gw. dec.state.ny.us*

Brad Gilbert
Clayton Environmental
400 Chastain Ctr. Blvd., NW
Suite 490
Kennesaw, GA 30144
tel: (770) 499-7500
fax: (770) 499-7511

Lester Grant
National Center for Environmental Assessment
US Environmental Protection Agency
MD-52
Research Triangle Park, NC 27711
tel: (919) 541-4173
fax: (919) 541-5078
email: *Grant.Lester@epa.gov*

Edward Green
Crowell & Moring LLP
1001 Pennsylvania Avenue, NW
Washington, DC 20004
tel: (202) 624-2922
fax: (202) 628-5116
email: *egreen@cromor.com*

Daniel S. Greenbaum
Health Effects Institute
955 Massachusetts Avenue
Cambridge, MA 02139
tel: (617) 876-6700
fax: (617) 876-6709
email: *dgreenbaum@healtheffects.org*

Wolfgang Groth
EEO Volkswagen of America, Inc.
3800 Hamlin Road
Mail Code 2E04
Auburn Hills, MI 48326
tel: (248) 340-4701
fax: (248) 340 -4707
email: *wolfgang.groth@vw.com*

D. Bruce Harris
ECPB
US Environmental Protection Agency
86 TW Alexander Drive, MD-61
Research Triangle Park, NC 27711
tel: (919) 541-7807
fax: (919) 541-7891
email: *dharris@engineer.aeerl.epa.gov*

Janet S. Hathaway
Natural Resources Defense Council
71 Stevenson Street, #1825
San Francisco, CA 94105-2939
tel: (415) 777-0220
fax: (415) 495-5996
email: *jhathaway@nrdc.org*

Michael Hawkins
Vehicle Environmental Engineering-Europe
Ford Motor Company, Ltd.
Brook Cottage
Elberton, South Gloucestershire
UK
tel: + 44 1454 418249
fax: + 44 1454 419339

Rowdy Heiser
Department of Mine Safety
FMC Corporation
P. O. Box 872
Green River, WY 82935
tel: (307) 872-2165
fax: (307) 872-2380
email: *Rowdy_Heiser@FMC*

Alain Henriet
Recherches et Affairs Scientifiques
PSA Peugeot Citroen
2, Route de Gisy
F-78140 Vélizy-Villacoublay Cedex
France
tel: + 33 141 36 29 30
fax: + 33 141 36 33 78
email: *a-henriet@calvanet.calvacom.fr*

Nobuyoshi Hirakochi
Truck & Bus Department
Mitsubishi Motors America, Inc
100 Center Square Road
P.O. Box 464
Bridgeport, NJ 08014-0464
tel: (609) 467-4664
fax: (609) 467-3919
email: *mrda2@snip.net*

Kent Hoekman
Chevron Products Company
575 Market Street
San Francisco, CA 94105
tel: (415) 894-3060
fax: (415) 894-2075
email: *skho@chevron.com*

David Hoel
Department of Biometry and Epidemiology
Medical University of South Carolina
155 Rutledge Avenue, Suite 1148
Charleston, SC 29425
tel: (843) 876-1152
fax: (843) 876-1127
email: *hoel@musc.edu*

Claire Holman
Senco
Brook Cottage, Elberton, Olveston
Bristol B535 4A0
UK
tel: + 44 1454 418247
fax: + 44 1454 419339
email: *cholman.senco@btinternet.com*

Larry Jones
ECPB
US Environmental Protection Agency
86 TW Alexander Drive, MD-61
Research Triangle Park, NC 27711
tel: (919) 541-7716
fax: (919) 541-0359
email: *ljones@engineer.aeerl.epa.gov*

Stuart Johnson
Environmental Office
Volkswagen
3800 Hamlin Rd
Auburn Hills, MI 48326
tel: (248) 340-4708
fax: (248) 340-4707
email: *stuart.johnson@vw.com*

Mark Kaszniak
IMC Global
2100 Sanders Road
Northbrook, IL 60062
tel: (847) 205-4856
fax:(847) 205-4921

Glenn Keller
Engine Manufacturers Association
401 North Michigan Avenue
Chicago, IL 60611
tel: (312) 644-6610
fax: (312) 321-5111
email: *glenn_keller@sba.com*

David Kittelson
Department of Mechanical Engineering
University of Minnesota
111 Church Street, SE
Minneapolis, MN 55455-0111
tel: (612) 625-1808
fax: (612) 624-1398
email: *kitte001@maroon.tc.umn.edu*

Jon Kogut
MSHA
US Department of Labor
P.O. Box 25367
Denver, CO 80225
tel: (303) 231-5593
fax: (303) 231-5542
email: *jkogut@msha.gov*

Peter Kohoutek
Group Research
Volkswagen AG
P.O. Box 1774
D-38436 Wolfsburg
Germany
tel: + 49 5361 76634
fax: + 49 5361 72960
email: *peter.kohoutek@volkswagen.de*

Don Kopinski
Engine Programs & Compliance Division
US Environmental Protection Agency
2000 Traverwood
Ann Arbor, MI 48105
tel: (734) 214-4229
fax: (734) 214-4816
email: *kopinski.donald@epa.gov*

Jane Koska
SHB
600 14th Street, NW
Suite 800
Washington, DC 20005
tel: (202) 662-4865
fax: (202) 783-4211

Linda Lance
White House Council on Environmental Quality
722 Jackson Place, NW
Washington, DC 20003
tel: (202) 395-5750
fax: (202) 456-6546
email: *Linda_Lance@ceq.eol.gov*

Henrik Landälv
Volvo Truck Corporation
Dept. 24440 (BC2)
SE-40508 Göteborg
Sweden
tel: + 46 31 66 5094
fax: + 46 31 66 55 20
email: *vtc.hlv@memo.volvo.se*

Douglas Lawson
National Renewable Energy Laboratory
1617 Cole Boulevard
Golden, CO 80401
tel: (303) 275-4429
fax: (303) 275-4415
email: *doug_lawson@nrel.gov*

David W. Layton
Earth and Environmental Sciences Directorate
Lawrence Livermore National Laboratory
P.O. Box 808 L-2867000 East Avenue
Livermore, CA 94551
tel: (925) 422-0918
fax: (925) 423-6785
email: *Layton1@llnl.gov*

Brian Leaderer
Department of Epidemiology and Public Health
Yale University School of Medicine
60 College Street
P.O. Box 208034
New Haven, CT 06520-8034
tel: (203) 785-2880
fax: (203) 737-6023
email: *brian.leaderer@yale.edu*

Nancy Lightfoot
Epidemiology Research Unit
Northeast Ontario Regional Caucer Centre
41 Ramsey Lake Road
Sudbury, Ontario P3E 5J1
Canada
tel: (705) 522-6237 ext 2650
fax: (705) 523-7337
email: *nlightfoot@neorcc.on.ca*

Michael Lipsett
OEHHA Air Pollution Epidemiology Section
California Environmental Protection Agency
1515 Clay Street, 16th Floor
Oakland, CA 94612
tel: (510) 622-3153
fax: (510) 622-3210
email: *mlipsett@berkeley.cahwnet.gov*

Larry Liukonen
TechCon, Inc.
1980 G Barrett
Mansfield, TX 76063
tel: (817) 453-0382
fax: (817) 453-0383
email: *techcon@flash.net*

Philip A. Lorang
Assessment and Modeling Division
US Environmental Protection Agency
2000 Traverwood Drive
Ann Arbor, MI 48105
tel: (734) 214-4374
fax: (734) 214-4821
email: *Lorang.phil@epa.gov*

Michael Madden
NEHEERL Human Studies Division
US Environmental Protection Agency
104 Mason Farm Road
Chapel Hill, NC 27599-7315
tel: (919) 966-6257
fax: (919) 966-6271
email: *madden.michael@epamail.epa.gov*

Joe L. Mauderly
Lovelace Respiratory Research Institute
2425 Ridgecrest Drive, SE
P.O. Box 5890
Albuquerque, NM 87108-5127
tel: (505) 845-1088
fax: (505) 845-1193
email: *Jmauderl@lrri.org*

Andreas C. R. Mayer
Technik Termische Maschinen
Fohrhölzlistrasse 14 b
CH-5443 Niederrohrdorf
Switzerland
tel: + 41 56 496 6414
fax: + 41 56 496 6415
email: *ttm.a.mayer@bluewin.ch*

Roger McClellan
Chemical Industry Institute of Toxicology
6 Davis Drive
P.O. Box 12137
Research Triangle Park, NC 27709-2137
tel: (919) 558-1202
fax: (919) 558-1400
email: *mcclellan@ciit.org*

Jim McGrath
National Center for Environmental Assessment, MD 52
US Environmental Protection Agency
Research Triangle Park, NC 27711
tel: (919) 541-0673
fax: (919) 541-1818

Daphne B. Moffett
NCEH/EHLS/Toxicology
Centers for Disease Control
4770 Buford Hwy, NE, MS F-17
Atlanta, GA 30341
tel: (770) 488-4107
fax: (770) 488-4609
email: *zzc0@cdc.gov*

Suresh Moolgavkar
Fred Hutchinson Cancer Center
1100 Fairview Avenue North, MP665
Seattle, WA 98109
tel: (206) 667-4273
fax: (206) 667-7004
email: *smoolgav@fhcrc.org*

Peter Morfeld
Institut für Arbeitswissenschaften
der RAG Aktiengesellach
Wengeplatz 1
D-44369 Dortmund
Germany
tel: + 49 231 3151 589
fax: + 49 231 3151 626
email: *ifarag@compuserve.com*

Pat Mulawa
Chemical and Environmental Sciences Lab
General Motors Research & Development Center
30500 Mound RD
MC 480-106-269
Warren, MI 48090
tel: (810) 986-1604
fax: (810) 986-1910
email: *pmulawa@notes.gmr.com*

Diane J. Mundt
Health Effects Institute
955 Massachusetts Avenue
Cambridge, MA 02139
tel: (617) 876-6700
fax: (617) 876-6709
email: *dmundt@healtheffects.org*

Kathleen Nauss
Health Effects Institute
955 Massachusetts Avenue
Cambridge, MA 02139
tel: (617) 876-6700
fax: (617) 876-6709
email: *knauss@healtheffects.org*

Margo T. Oge
Office of Mobile Sources
US Environmental Protection Agency
401 M. Street, SW
Washington, DC 20460
tel: (202) 260-7645
fax: (202) 260-3730

Robert O'Keefe
Health Effects Institute
955 Massachusetts Avenue
Cambridge, MA 02139
tel: (617) 876-6700
fax: (617) 876-6709
email: *rokeefe@healtheffects.org*

Jørgen H. Olsen
Institute of Cancer Epidemiology
Danish Cancer Society
Strandboulevarden 49
DK-2100 Copenhagen
Denmark
tel: +45 3525 7654
fax:+45 3525 7734
email: *jorgen@cancer.dk*

Bill Passie
Standards & Regulations
Catepillar Inc.
100 NE Adams Street
Peoria, IL 61628-7160
tel: (309) 675-5362
fax: (309) 675-6181
email: *passie_william.c@cat.com*

Chatur Patel
Engineering Dept.
Morton Salt
Morton International, Inc.
100 N. Riverside Plaza
Chicago, IL 60606-1597
tel: (312) 807-2695
fax: (312) 807-2040

James Pearson
Air Quality Lab
School of Civil and Environmental Engineering
Georgia Tech
Atlanta, GA 30332
tel: (404) 894-1753
fax: (404) 894-9223
email: *plumber@aql.eas.gatech.edu*

Steve Pezda
Vehicle Environmental Engineering
Ford Motor Company
17225 Federal Drive, Suite 145
Allen Park, MI 48101
tel: (313) 322-9213
fax: (313) 594-4271
email: *spezda@ford.com*

Claus Piekarski
Institute für Arbeitswissenschaften
der RAG Aktiengesellschaft
Wengeplatz 1
D-44369 Dortmund
Germany
tel: + 49-231-3151-564
fax: + 49-231-3151-626
email: *ifarag@compuserve.com*

Nils Plato
Department of Occupational Health
Karolinska Hospital
S-17176 Stockholm
Sweden
tel: + 46 8 51 77 32 62
fax: + 46 8 33 4333
email: *plato@ymed.ks.se*

Alison K. Pollack
ENVIRON Corporation
101 Rowland Way, Suite 220
Novato, CA 94945
tel: (415) 899-0700
fax: (415) 899-0707
email: *apollack@environ.org*

Charles Poole
Department of Epidemiology
School of Public Health
University of North Carolina at Chapel Hill
Box 740, McGavran-Greenberg Hall
Chapel Hill, NC 27599-7400
tel: (919) 966-9294
fax: (919) 966-2089
email: *cpoole@unc.edu*

Gurumurthy Ramachandran
Environmental and Occupational Health
School of Public Health
University of Minnesota
Box 807 Mayo
420 Delaware Street, SE
Minneapolis, MN 55455
tel: (612) 626-5428
fax: (612) 626-0650
email: *ram@cccs.umn.edu*

Martin Reape
Health Sciences Department
FMC Corporation
175 Market Street
Philadelphia, PA 19103
tel: (215) 299-6215
fax: (215) 299-6939
email: *martin_reape@fmc.com*

Jean Marie Revelt
Engine Programs and Compliance Division
US Environmental Protection Agency
2000 Traverwood
Ann Arbor, MI 48105
tel: (734) 214-4822
fax: (734) 214-4816
email: *revelt.jean-marie@epa.gov*

Charles Ris
Office of Research and Development
National Center for Environmental Assessment
US Environmental Protection Agency
Washington, DC 20460
tel: (202) 564-3203
fax: (202) 565-0077
email: *ris.charles@epa.gov*

E. Dean Roderique
Health/Safety Department
Morton International Corporation
100 North Riverside Plaza
Chicago, IL 60606
tel: (312) 807-3431
fax: (312) 807-3475
email: *Dean_Roderique@hub.morton*.com

Michael Rodgers
Air Quality Laboratory
School of Civil and Environmental Engineering
Georgia Tech
Atlanta, GA 30332
tel: (404) 894-5609
fax: (404) 894-9223
email: *mrodgers@aql.eas.gatech.edu*

Alan Rogers
Alan Rogers OH&S Pty Ltd
P. O. Box 2128
Clovelly 2031 New South Wales
Australia
tel: 61-2-9665-3558
fax: 61-2-9665-3558
email: *arogersohs@fastlink.com.au*

Isabelle Romiea
Centers for Disease Control and Prevention
2332 Massey, Mailstop F46
Atlanta, GA 20241-3724
tel: (770) 488-7649
fax: (770) 488-3506
email: *iar9@cdc.gov*

John C. Sagebiel
Desert Research Institute
2215 Raggio Parkway
Reno, NV 89512
tel: (775) 677-3196
fax: (775) 677-3303
email: *johns@dri.edu*

Thomas Sandstrom
Respiratory Medicine and Allergy
University Hospital of Umea
S-90185 Umea
Sweden
tel: + 46 90 785 2516
fax: + 46 90 141 369
email: *thomas_sandstrom@lung.umu.se*

Robert Säverin
Epidemiology Department
Federal Institute of Occupational Safety and Health
Noldner Strasse 40-42
D-10317 Berlin
Germany
tel: + 49 30 515 48 122
fax:+ 49 30 515 48 170
email: *saverin@baua.de*

Robert F. Sawyer
Department of Mechanical Engineering
University of California, Berkeley
72 Hesse Hall
Berkeley, CA 94720-1740
tel: (510) 642-4473
fax: (510) 642-1850
email: *rsawyer@euler.berkeley.edu*

Klaus-Peter Schindler
EAT
Volkswagen AG
Letter Box 1759
D-38436 Wolfsburg
Germany
tel: + 49 5361 922994
fax: + 49 5361 927362
email: *klaus-peter.schindler@volkswagen.de*

Richard Schreck
Analysis and Synthesis Department
General Motors
Technical Center MC 480-106-336M
30500 Mound Road
Warren, MI 48090-9055
tel: (810) 986-1742
fax: (810) 986-1647
email: *rschreck@notes.gmr.com*

Michael Schweizer
Emission Control Department
Mercedes-Benz of North America, Inc.
One Mercedes Drive
Montvale, NJ 07645
tel: (201) 573-2642
fax: (201) 573-6708
email: *schweizer@mbusa.com*

Debra Silverman
Occupational Epidemiology Branch EPN 418
Division of Cancer Etiology and Genetics
National Cancer Institute
6120 Executive Blvd
Room 8108
Bethesda, MD 20892
tel: (301) 435-4716
fax: (301) 402-1819
email: *silvermd@epndce.nci.nih.gov*

Thomas Sinks
Centers for Disease Control and Prevention
4770 Buford Highway, NE, MS F-29
Atlanta, GA 30341-3724
tel: (770) 488-7001
fax: (770) 488-7015
email: *ths2@cdc.gov*

Thomas J. Smith
Department of Environmental Health
Harvard School of Public Health
665 Hnntington Avenue
Boston, MA 02115
tel: (617) 432-3315
fax: (617) 432-0219
email: *tsmith@hohp.harvard.edu*

Heinrich Sönksen
Kali und Salz GmbH
Friedrich-Ebert Strasse 160
D-34119 Kassel
Germany
tel: + 49 561 301 1603
fax: + 49 561 301 1185

Michael F. Spallek
Health Services
Volkswagen AG
P.O. Box 21 05 80
D-30405 Hanover
Germany
tel: + 49 511 798 2109
fax: + 49 511 798 3366
email: *michael.spallek@volkswagen.de*

Frank E. Speizer
Channing Laboratory
Harvard Medical School
181 Longwood Avenue
Boston, MA 02115
tel: (617) 525-2275
fax: (617) 525-2066
email: *frank.speizer@channing.harvard.edu*

Dalia Spektor
Health Science & Technology Department
Rand
1700 Main Street
Santa Monica, CA 90407
tel: (310) 393-0411 ext 7840
fax: (310) 451-7062
email: *Dalia_Spektor@rand.org*

Rebecca Stanevich
National Institute for Occupational Safety and Health (NIOSH)
1095 Willowdale Road
Morgantown, WV 26505
tel: (304) 285-6218
fax: (304) 285-5820
email: *rssi@cdc.gov*

Kyle Steenland
International Agency for Research on Cancer
150 Cours Albert Thomas
69372 Lyon Cedex 08
France
tel: + 33 4 7273 8556
fax: + 33 4 7273 8342
email: *steenland@droopy.iarc.fr*

Eric Stine
Department of Toxicology & Health Risk Assessment
Chevron Research & Technology Co.
100 Chevron Way
Richmond, CA 94802
tel: (510) 242-4349
fax: (510) 242-7022
email: *rsti@chevron.com*

Jodi Sugerman-Brozan
Alternatives for Community and the Environment (ACE)
2343 Washington Street, 2nd Floor
Roxbury, MA 02119
tel: (617) 442-3343 ext 23
fax: (617) 442-2425
email: *jsuger@gis.net*

G. Marie Swanson
Michigan State University
Cancer Center
A-128 East Fee Hall
East Lansing, MI 48824-1316
tel: (517) 353-8828
fax: (517) 355-5126
email: *swansong@pilot.msu.edu*

Suzuki Tadao
Japan Automobile Research Institute
Health Effects Laboratory
2530 Karima
Tsukuba-shi, Tharaki 305-0822
Japan
tel: + 81 298 56 1111
fax: + 81 298 55 2922
email: *tsuzuki@jari.or.jp*

Jeff Terry
Engine Manufacturers Association
401 N. Michigan Ave.
Chicago, IL 60611
tel: (312) 644-6610 ext 3821
fax: (312) 321-5111
email: *jterry@sba.com*

Pramod Thakur
Research and Development Dept.
CONSOL Inc.
1027 Little Indian Creek Road
Morgantown, WV 26501
tel:(304) 983-3207
fax: (304) 983-3209
email: *pramodthakur@consolcoal.com*

Thomas Tomb
PSHTC/Dust Division
MSHA
US Department of Labor
Cochrans Mill Road
Building 38, Room 106
Pittsburgh, PA 15236
tel: (412) 892-6859
fax: (412) 892-6948
email: *tombtf@msha.gov*

Daniel Tosteson
Cell Biology
Harvard Medical School
220 Longwood Ave
Goldenson Building, Room 243
Boston, MA 02115
tel: (617) 432-3660
fax: (617) 432-3662

Melinda Treadwell
NESCAUM
129 Portland Street, 5th Floor
Boston, MA 02114
tel: (617) 367-8540
fax: (617) 742-9162
email: *mtreadwell@nescaum.org*

Thomas Trueblood
Public Affairs Dept.
Navistar International Transportation Corp
455 N. Cityfront Plaza Drive
Chicago, IL 60611
tel: (312) 836-2646
fax: (312) 836-3982
email: *thomas.trueblood@navistar.com*

Lorraine Twerdok
Health & Environmental Sciences Dept.
American Petroleum Institute
1220 L Street, NW
Washington, DC 20005
tel: (202) 682-8344
fax: (202) 682-8270
email: *Twerdokl@api.org*

Gerald van Belle
National Research Center for Statistics
and the Environment
University of Washington
Room 401 Bagley Hall
Box 351720
Seattle, WA 98195-1720
tel: (206) 616-9262
fax: (206) 616-9443
email: *vanbelle@u.washington.edu*

Dave Verma
Program in Occupational Health and
Environmental Medicine
McMaster University
1200 Main Street West, HSC-3H51
Hamilton, Ontario L8N 3Z5
Canada
tel: (905) 525-9140 ext 22792
fax: (905) 528-8860
email: *vermadk@mcmaster.ca*

Jaro J. Vostal
Environmental Health Assessment
Corporation International
6360 Hills Drive
Bloomfield Hills, MI 48301
tel & fax: (248) 644-6527
email: *ehacvostal@sprintmail.com*

Vanessa T. Vu
National Center for Environmental Assessment
(8601D)
US Environmental Protection Agency
Office of Research and Development
401 M Street, SW
Washington, DC 20460
tel: (202) 564-3282
fax: (202) 565-0066
email: *vu.vanessa@epa.gov*

Christine Vujovich
Bus, Light Commercial, Automotive &
Environmental Management
Cummins Engine Company
500 Jackson Street
MC 60616
Columbus, IN 47201
tel: (812) 377-3101
fax: (812) 377-3082
email: *cmvujovich@cob.cummins.com*

John C. Wall
Research & Development
Cummins Engine Company
Box No. 3005
Columbus, IN 47202
tel: (812) 377-7344
fax: (812) 377-7050
email: *John.C.Wall@ CTC.Cummins.com*

Jane Warren
Health Effects Institute
955 Massachusetts Avenue
Cambridge, MA 02139
tel: (617) 876-670
fax: (617)876-6709
email: *jwarren@healtheffects.org*

Urban Wass
Environmental Science Dept.
Volvo
S-40508 Gothenburg
Sweden
tel: + 46 31 595290
fax: + 46 31 546188
email: *tu.wass@memo.volvo.se*

Jim Weeks
Department of Occupational &
Environmental Health
United Mine Workers
George Washington University
2300 K Street, NW, Suite 201
Washington, DC 20037
tel: (202) 994-6123
fax: (202) 994-0011
email: *eohjlw@gwumc.edu*

Dane Westerdahl
California Air Resources Board
2020 L Street
Sacramento, CA 95614
tel: (916) 323-1522
fax: (916) 322-4357
email: *fwesterd@arb.ca.gov*

Stephanie Williams
Department of Environmental Affairs
California Trucking Association
3251 Beacon Blvd.
West Sacramento, CA 95691
tel: (916) 373-3548
fax: (916) 371-7346
email: *swilliams@calrux.org*

Harold Wimette
DaimlerChrysler
Environmental and Energy Affairs
CIMS 482-00-71
800 Chrysler Drive
Auburn Hills, MI 48326-2753
tel: (248) 576-5505
fax: (248) 576-7928
email: *hjw4@daimlerchrysler.com*

Susan Woskie
Department of Work Environment
University of Massachusetts, Lowell
One University Avenue
Lowell, MA 01854
tel: (978) 934-3295
fax: (978) 452-5711

Charles M. Yarborough
Caterpillar, Inc.
100 Northeast Adams Street, #1410
Dunlap, IL 61629
tel: (309) 675-5174
fax: (309) 675-1076
email: *yarborough_charles_m@cat.com*

Daniel Yereb
ORDS
National Institute of Occupational Health and
Safety (NIOSH)
1095 Willowdale Road
Morgantown, WV 26505
tel: (304) 285-6146
fax: (304) 285-5820
email: *dsy0@cdc.gov*

Barbara Zielinska
Desert Research Institute
2215 Raggio Parkway
Reno, NV 89512-1095
tel: (702) 677-3198
fax: (702) 677-3157
email: *barbz@dri.edu*

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Health Effects Institute

955 Massachusetts Avenue
Cambridge, MA 02139

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