HEALTH EFFECTS INSTITUTE

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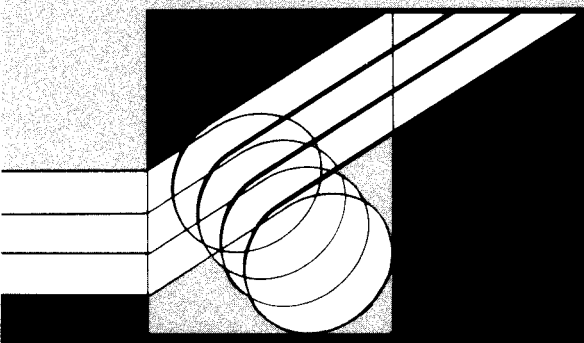
NEW INVESTIGATOR PROGRAM

RESEARCH REPORT No. 6



Effect of Nitrogen Dioxide, Ozone, and Peroxyacetyl Nitrate On Metabolic and Pulmonary Function

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Includes the Report of the Institute's Health Review Committee

The Health Effects Institute (HEI) is a non-profit corporation founded in 1980 to assure that objective, credible, high-quality scientific studies are conducted on the potential human health effects of motor vehicle emissions.

Funded equally by the U.S. Environmental Protection Agency (EPA) and 26 automotive manufacturers or marketers in the United States, HEI is independently governed. Its research projects are selected, conducted, and evaluated according to a careful public process, including a rigorous peer review process, to assure both credibility and high scientific standards.

HEI makes no recommendations on regulatory and social policy. Its goal, as stated by former EPA Administrator William D. Ruckelshaus, is "simply to gain acceptance by all parties of the data that may be necessary for future regulations."

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PREFACE

THE HEALTH EFFECTS INSTITUTE AND ITS RESEARCH PROCESS

The Health Effects Institute (HEI) is an independent nonprofit corporation which, according to its charter, is "organized and operated . . . specifically to conduct or support the conduct of, and to evaluate, research and testing relating to, the health effects of emissions from motor vehicles."

It is organized in the following ways to pursue this purpose:

INDEPENDENCE IN GOVERNANCE

HEI is governed by a four-member board of directors whose members are William O. Baker, Chairman Emeritus of Bell Laboratories and Chairman of the Board of Rockefeller University; Archibald Cox, Carl M. Loeb University Professor (Emeritus) at Harvard University; Donald Kennedy, President of Stanford University; and Charles Powers, President, Clean Sites, Incorporated. Professor Cox chairs the Board. These individuals, who select their own successors, were chosen initially, after consultations with industry and other individuals, by then Environmental Protection Agency Administrator, Douglas M. Costle.

TWO-SECTOR FINANCIAL SUPPORT

The Institute receives half of its funds from the United States government through the Environmental Protection Agency and half from the automotive industry. Twenty-six leading manufacturers of vehicles or engines that are certified for use on U.S. highways contribute to the Institute's budget, in shares proportionate to the number of vehicles or engines that they sell.

RESEARCH PLANNING AND PROJECT EVALUATION

HEI is structured to define, select, support, and review research that is aimed at investigating the possible health effects of mobile source emissions. Its research program is devised by the Health Research Committee, a multidisciplinary group of scientists knowledgeable about the complex problems involved in determining the health effects of mobile source emissions. The Committee seeks advice from HEI's sponsors and from other sources prior to independently determining the research priorities of the Institute.

After the Health Research Committee has defined an area of inquiry, the Institute announces to the scientific community that research proposals are being solicited on a specific topic. Applications are reviewed first for scientific quality by an appropriate expert panel. Then they are reviewed by the Health Research Committee both for quality and for relevance to the mission-oriented research program. Studies recommended by the Committee undergo final evaluation by the Board of Directors, which also reviews the procedures, independence, and quality of the selection process.

When a study is completed, a draft final report is reviewed by a separate HEI Committee, the Health Review Committee. Members are expert scientists representing a broad range of experience in environmental health sciences. The Review Committee has no role in the review of applications or the selection of projects and investigators for funding. This Committee assesses the scientific quality of each study and evaluates its contribution to unresolved scientific questions.

Each funded proposal is assigned in advance of completion to a member of the Review Committee, who acts as "primary reviewer". When the draft report is received, the primary reviewer directs a peer review that involves: (1) referral of the report to appropriate technical experts and, when appropriate, (2) involvement of the Review Committee biostatistician to determine the appropriateness of the statistical methods used to evaluate the data. After the investigator has had a chance to comment on the technical evaluations, the primary reviewer drafts a review. This document is sent to the investigator for comment and subsequently is examined by the full Review Committee and revised as necessary. The investigator's final report as well as the Review Committee's report, are then made available to the sponsors and to the public after evaluation by the HEI Board of Directors.

All HEI investigators are urged to publish the results of their work in the peer-reviewed literature. The timing and nature of HEI report releases are tailored to ensure that the Review Committee's report does not interfere with the journal publication process. The report of the Review Committee will be as thorough as necessary to evaluate any individual report.

INTRODUCTION

A Request for Applications (RFA 82-7), soliciting proposals from new investigators on research topics relevant to health effects from motor vehicle emissions, was issued in the summer of 1982. The purpose of setting up a "new investigator program" was to encourage new investigators, who were at a stage in their careers comparable to that of an assistant professor, to undertake research on important questions concerning potential adverse health consequences from automotive-generated air pollution.

In the fall of 1982, Dr. Deborah M. Drechsler-Parks of the University of California at Santa Barbara proposed a project, entitled "Effect of NO_2, O_3, and PAN on Pulmonary and

Metabolic Function". HEI approved the two-year investigatorship and authorized a total expenditure of $73,000. The project began in September 1983, and the final report was accepted by the Health Review Committee in October 1986. The Health Review Committee's report, which follows the investigator's report, is intended to place the investigator's final report in perspective as an aid to the sponsors of HEI and to the public.

THE CLEAN AIR ACT

Under the Clean Air Act, as amended (1)†, EPA has broad authority to adopt emission standards for, *inter alia*, new motor vehicles (2)†, and any source of a "hazardous" air pollutant (one that may cause "an increase in mortality or an increase in serious irreversible, or incapacitating reversible, illness") (3)†. EPA may regulate the contents of motor vehicle fuels (4)†. In an emergency, in the absence of adequate state or local action, EPA may sue to enjoin any emissions contributing to "an imminent and substantial endangerment to the health of persons" (5)†. EPA also establishes national ambient air quality standards for so-called "criteria" air pollutants (6)†. In making public health assessments and judgements in connection with the exercise of these powers, EPA considers, *inter alia*, the exposure of human beings to the substance at issue and its toxicity to exposed individuals. Research bearing on such exposure or toxicity is, therefore, relevant to the exercise of EPA's regulatory authorities.

BACKGROUND

Chamber experiments, in which human subjects are exposed to controlled concentrations of specific air pollutants, are an accepted means of studying acute health effects. Most studies, however, have focused on a single pollutant, although a few have examined combinations of two compounds. Given the complex nature of the typical urban atmosphere, it is clearly important to understand the potential health effects that may be caused by breathing such a complex mixture. Furthermore, because most of the available data are for young men, it is also important to study the age-related and sex-related consequences of air pollution exposures.

Ozone (O_3), nitrogen dioxide (NO_2), and peroxyacetyl nitrate (PAN) are important constituents of photochemical smog. Nitrogen oxides are emitted directly into the air in motor vehicle exhaust, and O_3 and PAN are photochemical oxidants that result from the reaction of nitrogen oxides and hydrocarbons in the presence of sunlight. Available evidence suggests that at ambient concentrations, NO_2 and PAN do not affect pulmonary function significantly, although O_3 has been shown to cause significant decrements in pulmonary functions at levels close to the existing National Ambient Air Quality Standard. Moreover, the effects of O_3 are exacerbated by exercise.

In her experiments, Dr. Drechsler-Parks exposed 32 nonsmoking men and women (half between the ages of 18 and 26, and half between the ages of 51 and 76) to combinations of O_3, NO_2, and PAN. She then examined the changes in metabolic and pulmonary function that occurred in response to these exposures.

† **Refer to Notes on page 36.**

INVESTIGATOR'S REPORT

by Deborah M. Drechsler-Parks

Effect of Nitrogen Dioxide, Ozone, and Peroxyacetyl Nitrate on Metabolic and Pulmonary Function

ABSTRACT

The metabolic and pulmonary function responses were investigated in 32 non-smoking men and women (8 men and 8 women 18-26 years of age, and 8 men and 8 women 51-76 years of age) who were exposed for 2 hours to each of 8 conditions: 1) filtered air (FA), 2) 0.13 ppm peroxyacetyl nitrate (PAN), 3) 0.45 ppm ozone (O_3), 4) 0.60 ppm nitrogen dioxide (NO_2), 5) 0.13 ppm PAN + 0.45 ppm O_3 (PAN/O_3), 6) 0.13 ppm PAN + 0.60 ppm NO_2 (PAN/NO_2), 7) 0.60 ppm NO_2 + 0.45 ppm O_3 (NO_2/O_3), and 8) 0.13 ppm PAN + 0.60 ppm NO_2 + 0.45 ppm O_3 (PAN/NO_2/O_3). The subjects alternated 20-min periods of rest (n = 3) and cycle ergometer exercise (n = 3) at a work load predetermined to elicit a ventilatory minute volume ($\dot{V}_E$) of approximately 25 L/min (BTPS). Functional residual capacity (FRC) was determined pre- and post-exposure. Forced vital capacity (FVC) was determined before and after exposure, and 5 min after each exercise period. Heart rate was monitored throughout each exposure, and $\dot{V}_E$ was measured during the last 2 min of each exercise period.

Exposure to FA, PAN, NO_2, and PAN/NO_2 had no effect on any measure of pulmonary or metabolic function. Ozone was primarily responsible for the pulmonary function effects observed. There was no significant difference between the responses to O_3 exposure and the responses to the three O_3 mixtures, indicating no interactions between the pollutants. The results suggest that women may be somewhat more responsive to O_3 exposure than men, and that older people (51-76 years of age) may be less responsive to O_3 than younger people (18-26 years of age).

INTRODUCTION

Generally research has focused on the health effects of individual entities found in polluted air. Little information is available regarding the health effects of mixtures of pollutants. Since many of the more abundant air pollutants are chemically highly reactive, and since many pollutants occur concurrently in ambient air, it is possible that two or more pollutants could interact in ambient air and cause effects which could not be predicted from the effects observed with the individual pollutants.

Nitrogen dioxide (NO_2) is one of the more abundant air pollutants, and is a major precursor for the photosynthetic formation of the photochemical oxidants ozone (O_3) and peroxyacetyl nitrate (PAN). The effects, particularly the pulmonary function effects, of exposure to each of these three pollutants individually have been investigated to varying degrees. At ambient levels (less than 1 ppm for NO_2, and less than 0.3 ppm for PAN) NO_2 and PAN appear to have insignificant effects on metabolic and pulmonary function (Drechsler-Parks et al., 1984; Folinsbee et al., 1978b; Gliner et al., 1975; Horvath et al., 1978, 1986; Raven et al., 1974a, 1974b, 1976). Ozone, however, has been shown to induce significant decrements in various measures of pulmonary function, including forced vital capacity (FVC), timed forced expiratory volume (FEV_t), forced expiratory flow rate between 25% and 75% of vital capacity (FEF25-75%), and inspiratory capacity (IC) at ambient levels (i.e., up to about 0.75 ppm) (Bates et al., 1972; Folinsbee et al., 1978a; Hazucha et al., 1973; Young et al., 1964). The effects of O_3 are exacerbated by exercise (Folinsbee et al., 1975; Folinsbee et al., 1977).

There have been investigations into the effects of exposure to only a few mixtures of oxidant air pollutants. Recent work in our laboratory investigated the metabolic and pulmonary function responses of young men (Drechsler-Parks et al., 1984), and young women (Horvath et al., 1986), to exposure to the combination of 0.45 ppm O_3 and 0.30 ppm PAN (PAN/O_3), compared to exposure to 0.30 ppm PAN and 0.45 ppm O_3 singly. The results of both studies suggested that PAN and O_3 interacted, in that exposure to PAN/O_3 induced mean decrements in pulmonary function which were approximately 10% larger than exposure to O_3 alone. Exposure to PAN alone induced no changes in pulmonary function.

There have been some investigations into the effects of exposure to mixtures of NO_2 and O_3 (Folinsbee et al., 1981; Hackney et al., 1975a, 1975b; Horvath et al., 1978, 1979). These reports suggest that the effects of exposure to this mixture are no greater than can be accounted for by the O_3 concentration. Responses to mixtures of PAN and NO_2, or PAN, NO_2, and O_3 have not yet been evaluated.

These results suggested that the effects of exposure to more complex mixtures which include O_3 was warranted, since polluted ambient air contains many different pollutants, some of which are at least potentially able to interact. Since NO_2 is a precursor for the photosynthetic formation of both O_3 and PAN, it seemed that addition of NO_2 to the exposure mixture was the logical step for extending our past work.

To date, most investigations into air pollutant exposure effects have been conducted with only young men as subjects,

with the data base on young women being more limited than that on young men. There have been no published reports regarding the responses of healthy middle-aged and older men and women to oxidant pollutant exposure.

SPECIFIC AIMS

Therefore there were three purposes for this study: 1) to compare the responses of men and women to oxidant pollutant exposure. 2) to compare the responses of men and women between 18 and 30 years of age with those of men and women over 50 years of age, and 3) to investigate possible interactions between O_3, NO_2 and PAN, i.e. does exposure to mixtures of O_3, NO_2 and PAN induce the same or different effects than those which would be expected from the sum of the responses to exposure to each of these pollutants separately?

MATERIALS AND METHODS

Thirty-two healthy non-smokers (8 men and 8 women between 18 and 26, and 8 men and 8 women between 51 and 76 years of age) volunteered as subjects for this study (Table 1). The purpose, attendant risks, and benefits of the study were explained verbally and given on a written form to each subject prior to his/her voluntary consent to participate. The protocol and procedures were approved by the UCSB Committee on Activities Involving Human Subjects. Each potential subject was interviewed by the principal investigator, and was screened by medical history, resting 12-lead electrocardiogram, a battery of clinical pulmonary function tests, and a submaximal exercise test. Only volunteers with normal pulmonary and cardiac function were accepted as subjects. None had a history of asthma. All subjects resided in an area with low outdoor ambient pollution levels.

All subjects were paid volunteers who came from a variety of sources. All would be classified as middle-class Caucasians. Except for one young man (a jet aircraft mechanic), the young men and women were students at the University of California, Santa Barbara. The older subjects, most of whom were retired, included several housewives, two meteorologists, a professional cellist, several engineers of various specialties, and two UCSB employees (one from the Registrar's Office, and a scientific instruments technician). Most of the subjects participated regularly in some form of exercise, including gardening, jogging, bicycling, swimming, tennis, or an organized exercise class. One older man was a marathon runner, and one of the young men participated in the triathalon. The other subjects would be classified as moderately fit.

The subjects were exposed in random order to each of eight conditions (Table 2): (1) filtered air (FA), (2) 0.13 ppm PAN, (3) 0.45 ppm O_3, (4) 0.60 ppm NO_2, (5) 0.13 ppm PAN + 0.45 ppm O_3 (PAN/O_3), (6) 0.13 ppm PAN + 0.60 ppm NO_2 (PAN/NO_2), (7) 0.60 ppm NO_2 + 0.45 ppm O_3 (NO_2/O_3), and (8) 0.13 ppm PAN + 0.60 ppm NO_2 + 0.45 ppm O_3 (PAN/NO_2/O_3). The exposures were separated by a minimum of a week. The O_3 concentration is approximately at the third stage alert level, and was so chosen to be comparable to past work from our laboratory, and to the work of others, while insuring a response with minimum irritation to the subjects. The PAN concentration is somewhat higher than daily mean concentrations that generally occur, though it is lower than peak levels which have been measured in some areas of Southern California (Grosjean, 1984). The PAN concentration was intentionally chosen to be lower than in our previous studies at 0.24 to 0.30 ppm (Drechsler-Parks et al., 1984; Gliner et al., 1975; Horvath et al., 1986; Raven et al., 1974a, 1974b, 1976) so that we could investigate whether or not the interaction we previously observed (Drechsler-Parks et al., 1984; Horvath et al., 1986) with simultaneous PAN/O_3 exposure with the PAN concentration at 0.30 ppm was also evident at a level more comparable to commonly occurring mean daily levels. The NO_2 concentration was toward the high end of the range of actual ambient NO_2 concentrations (EPA, 1982).

The exposures were carried out in a 1.75 x 1.75 x 2.24 m double-walled acrylic chamber. Inlet air was chemically and mechanically filtered to Class 100 purity prior to entering the chamber and was exhausted to the roof. The chamber air turnover time was approximately 2.5 min. Ambient temperature in the chamber was 19°C WBGT (Wet Bulb Globe Temperature = 0.7 $T_{wet\ bulb}$ + 0.3 $T_{globe\ or\ dry\ bulb}$) (Table 2).

During each exposure the subjects alternated 20-min periods (n = 3) of rest and 20-min periods (n = 3) of exercise on a cycle ergometer at a work load sufficient to yield a ventilatory minute volume ($\dot{V}_E$) of approximately 25 L/min (BTPS). The appropriate work load for each subject was determined prior to the first experiment. The work loads ranged from no resistance on the ergometer to 450 kgm/min, depending on the physical fitness level of the subject.

Functional residual capacity (FRC) was determined prior to and immediately after each exposure by the helium dilution method on a 13.5-L Benedict-Roth type spirometer (W. E. Collins, Braintree, MA). Residual volume (RV) and expiratory reserve volume (ERV) were calculated from the FRC recordings. Three FVC maneuvers were recorded before the exposure began, and also at 5 min after each exercise period, on a rolling seal type spirometer (model 822, Ohio Medical, San Leandro, CA) which was interfaced with a microprocessor (Spirotech 300, Spirotech, Inc., Atlanta, GA), which provided (in addition to predicted values for each) the following information for each test maneuver: FVC, $FEV_{0.5}$, $FEV_{1.0}$, $FEV_{3.0}$, FEF25-75%, peak flow rate, forced expiratory flow at 25%, 50% and 75% of FVC (FEF25%, FEF50% and FEF75%). All volumes were corrected to BTPS. Pulmonary function tests were performed in the standing position.

Ventilatory minute volume ($\dot{V}_E$) was measured during the last 2 min of each exercise period by having the subjects breathe through a mouthpiece/valve assembly. Inspired air

Table 1: Characterization of the four subject groups

	Age yr	Height cm	Weight kg	BSA m^2	FVC L	%Pred.* FVC	$FEV_{1.0}$ L	%Pred.* $FEV_{1.0}$
Young Men								
$\bar{X}$	21.8	177.8	74.0	1.90	5.60	99	4.58	101
SD	2.1	10.5	9.9	0.17	1.02	13	0.92	16
Range	19-26	160.8-188.2	52.3-87.3	1.53-2.09	3.79-6.85	83-116	3.13-5.40	70-115
Older Men								
$\bar{X}$	61.2	177.9	78.5	1.96	4.97	107	3.81	117
SD	6.2	6.7	5.1	0.08	0.53	5	0.57	11
Range	51-69	171.4-190.4	70.7-83.8	1.87-2.13	4.41-6.17	99-117	3.13-4.96	106-138
Young Women								
$\bar{X}$	20.5	165.9	62.3	1.68	4.21	100	3.63	107
SD	1.2	6.0	8.9	0.11	0.60	8	0.42	9
Range	19-22	155.8-176.6	50.7-75.2	1.56-1.86	3.14-5.21	84-111	2.73-4.06	89-116
Older Women								
$\bar{X}$	64.5	163.1	60.8	1.64	3.11	104	2.43	112
SD	6.3	4.8	9.8	0.15	0.49	13	0.41	17
Range	56-76	155.7-170.5	45.6-77.8	1.42-1.90	2.59-3.78	84-123	2.00-2.92	86-137

*From Cherniack et al., 1972; Dickman et al., 1971; Gaensler 1951; Morris et al., 1971

Table 2: Characterization of the eight exposures

Exposure	FA	PAN	O_3	NO_2	PAN/O_3	PAN/NO_2	NO_2/O_3	PAN/NO_2/O_3
WBGT (°C)*	19.4	19.7	19.1	19.1	19.5	19.4	18.8	19.6
± SD	1.9	1.6	1.9	1.9	2.5	1.6	2.3	2.0
PAN (ppm)		0.127			0.132	0.130		0.135
± SD		0.006			0.014	0.010		0.014
NO_2 (ppm)				0.600		0.606	0.595	0.604
± SD				0.008		0.010	0.009	0.009
O_3 (ppm)			0.454		0.454		0.452	0.448
± SD			0.005		0.006		0.008	0.010
$T_{dry\ bulb}$ (°C)	24.2	24.6	24.0	24.0	24.0	24.5	24.0	24.4
± SD	1.4	1.4	1.2	1.3	1.8	1.3	1.1	1.3
RH (%)	58	54	58	57	58	52	55	56
± SD	9	11	8	8	10	9	10	10

*WBGT = Wet Bulb Globe Temperature
= 0.7 $T_{wet\ bulb}$ + 0.3 $T_{dry\ bulb\ or\ globe}$

was from the chamber, and the expired air was directed through a Parkinson-Cowan dry gas meter which was electronically interfaced with a strip-chart recorder. It should be noted that the subjects only breathed through the mouthpiece for about 3 min out of each exercise period, or a total of 9 min out of each 2-hour exposure.

Ventilatory minute volume ($\dot{V}_E$) was not measured during rest periods. Resting values of 8.0 L/min for men, and 7.0 L/min for women (Thorn et al., 1977) were used for calculating the estimated effective doses of the pollutants. Heart rate was monitored throughout each exposure, and was recorded at 5-min intervals during exercise. Respiratory rate was obtained from the $\dot{V}_E$ records.

Following each exposure the subjects were asked to complete a written questionnaire on which were listed a number of symptoms commonly associated with exercise and/or air pollutant exposure. Symptom severity was not rated, subjects were asked to respond "yes" or "no" as to whether or not they experienced each listed symptom. The symptom data are reported as the number of subjects who reported "yes" for each given symptom.

Ozone was generated from 100% oxygen by two ultraviolet ozone generators (Ozone Research & Equipment Corp., Phoenix, AZ) and was added via the chamber air intake duct. The chamber O_3 concentration was continuously monitored by an ultraviolet absorption O_3 analyzer (Dasibi Environmental Corp., Model 1003-AH, Glendale, CA), which was annually calibrated against a standard ozone photometer (Dasibi) by the California Air Resources Board (El Monte, CA). There were no deviations in zero and span from one calibration to the next which were large enough to affect the accuracy of the O_3 concentration readings. The Dasibi O_3 analyzer is constructed so that the zero and/or span must be seriously off-calibration before the output concentration readings are affected. The Dasibi electronics include an internal correction mechanism which compensates for deviations from perfect calibration over a wide range.

The PAN was purchased as approximately 1000 ppm PAN in N_2 from the Statewide Air Pollution Research Center at the University of California, Riverside, and was stored at 8°C to minimize decomposition. It was introduced through Teflon tubing to the chamber air intake duct. The PAN concentration in the exposure chamber was determined every 10 min by electron capture vapor phase gas chromatography (Varian Aerograph, 600D, Palo Alto, CA) on an aliquot of chamber air. Source tanks of PAN were analyzed by infrared absorption (Perkin-Elmer, 683, Perkin-Elmer, Ltd., Buckinghamshire, England) prior to each experimental exposure (Maynsohn et al., 1965, Stephens 1964; Stephens et al., 1973).

Nitrogen dioxide was purchased as 1% NO_2 in nitrogen, and was added through Teflon tubing via the chamber air intake duct. The chamber NO_2 concentration was monitored with a chemiluminescent NO_x analyzer (Thermo-Electron Corp., 14B/E, Hopkinton, MA) which was annually calibrated by the California Air Resources Board (El Monte, CA), and checked weekly for zero and span.

There is potential in multiple pollutant studies for the individual pollutants to affect the operation and output of analyzers which measure other pollutants being used in the study. We investigated whether or not this type of interference occurred with O_3, NO_2 and PAN in the present study, and if so, how significant an error was introduced.

It has been reported previously (Grosjean et al., 1984; Winer et al., 1974) that chemiluminescent NO_x analyzers respond on the NO_2 channel to PAN. We also observed this on the NO_2 channel of our NO_x analyzer, and conducted the following investigation into the probable magnitude of the interference it introduced into the NO_2 concentration measurements during exposures containing both PAN and NO_2.

The exposure chamber was set up as if an actual exposure was to occur; that is, the airflow system was on, and all analyzers were operating in place, though no subjects were in the chamber. A steady flow of PAN was introduced into the chamber. Within 5 min the PAN concentration reached an equilibrium of 0.13 ppm, as measured by gas chromatography. The NO_2 analyzer indicated a concentration of 0.11 ppm, even though no NO_2 was entering the chamber. Next, NO_2 was introduced into the chamber until the NO_2 analyzer indicated an equilibrium NO_2 concentration of 0.60 ppm, at which time the PAN flow was discontinued. The NO_2 concentration then dropped 0.07 ppm, or about 60% of the actual PAN concentration, and then stabilized at 0.53 ppm NO_2, suggesting that the actual NO_2 concentration during exposures containing both PAN and NO_2 may be approximately 0.07 ppm lower than indicated on the NO_2 analyzer. There was no interaction of PAN or NO_2 on the O_3 analyzer, nor was there an effect of O_3 on the NO_2 or PAN analyzers.

When both NO_2 and O_3 were in the exposure chamber there was some consumption of O_3 by NO_2. The consumption was evaluated in the following manner. The chamber was set up as if an actual exposure was to occur; that is, all analyzers were operating and the airflow system was in operation, though no subjects were in the chamber. Inflow of NO_2 and O_3 was initiated, and the chamber was equilibrated at an NO_2 concentration of 0.590 ppm, and an O_3 concentration of 0.464 ppm. The NO_2 inflow was then discontinued, and the O_3 concentration was monitored for 25 min (50 measurement cycles on the Dasibi analyzer). Once the NO_2 inflow ceased, the O_3 concentration began to rise, until at the 50th measurement cycle the O_3 concentration was 0.538 ppm. No adjustments to the O_3 generation or inflow rates were made. When NO_2 inflow was resumed, the NO_2 concentration increased, and the O_3 concentration decreased toward the initial values. During actual experiments, inflow rates for NO_2 and O_3 could be found where fluctuations in the NO_2 and O_3 concentrations were minimal.

We also investigated whether or not there was formation of particles of 1 micron or less in diameter under experimental conditions (with subjects in the chamber) by performing particle counts during actual exposures with each of the pollutant mixtures. No detectable particles were found in the size range of 0.0032 to 1.0 microns. While particle formations is possible under some of the exposure conditions of this study, the failure to detect small particles suggests that the airflow rate through the chamber was sufficient to preclude formations in the chamber of particles small enough that they would penetrate deeply into the lung. Our particle analyzer did not have the capability to count particles larger than 1 micron; however, particles this large are largely filtered out in the nose and upper airways.

The symptom data were analyzed with the Cochran Q-test (Siegal, 1956). This test provides a method for testing whether or not the responses of the subjects to each symptom question are the same or different for the eight ambient conditions. A finding of statistical significance indicates that the subjects gave different responses for a given symptom across the eight exposures.

Pulmonary function data analysis was by analysis of variance with two grouping factors (sex and age) and two repeated measures factors (exposure and time period). Preliminary work with the pulmonary function data revealed that the wide range of lung sizes among the subjects resulted in large standard deviations. Consequently large percentage pre- to post-exposure changes could occur and yet not be statistically significant. We therefore normalized the data to the form of percent change from pre- to post-exposure in order to at least partially remove the effect of absolute lung size, and thereby allow a better comparison of the four subject groups. When significant differences were found, a further analysis of simple main effects, followed by the Tukey multiple comparison procedure (Neter et al., 1974), was employed to determine significant interactions.

The pulmonary function data were also analyzed with a 2^5-factorial analysis of variance design. This model has five factors (age group, sex, O_3, NO_2 and PAN), with two levels of each. The model, then, analyzes for a main effect for sex, age, and for each of the three pollutants, and tests all possible combinations of factors for interaction effects. This model does not require any *post-hoc* tests since all possible combinations of factors are covered by the five-factor design, in contrast to the repeated measures design described above, which has one exposure factor with eight levels, and does require *post-hoc* tests to differentiate among the various exposures.

RESULTS

The mean percentage changes from pre- to post-exposure in FVC, $FEV_{1.0}$, $FEV_{3.0}$, FEF25-75% and FEF75% are shown in Tables 3 to 7 (mean + SE) grouped by age and sex, by sex only, and by age only within each table. Note that a negative sign indicates an *increase* at post-exposure. Analysis of variance tables are available in Appendix I.

When the data were analyzed as the percentage change from pre- to post-exposure, there was no difference between the responses of men and women in any measure of pulmonary function, although the absolute volume changes in women were less than those in men. Regardless of sex, the older subjects had significantly ($p < 0.01$) smaller changes in FVC, $FEV_{1.0}$, $FEV_{3.0}$ and FEF25-75% than the younger subjects. There were no significant differences ($p > 0.05$) between the older and younger subjects in FEF75%, ERV, RV or FRC.

Subject groups (without regard for age or sex) had significant ($p < 0.01$) decrements in FVC, $FEV_{1.0}$, $FEV_{3.0}$, FEF25-75% and FEF75% consequent to exposure to O_3 and the three O_3-containing mixtures. However, there were no differences between the responses induced by these four exposures. There were no changes ($p > 0.05$) in any measure of pulmonary function with FA, PAN, NO_2 or PAN/NO_2 exposure for any group.

The only significant interaction ($p < 0.04$ or better) was between age and exposure. An analysis of main effects plus the Tukey procedure showed that the older subjects had no significant ($p > 0.05$) changes in $FEV_{3.0}$, FEF25-75% or FEF75% with any of the eight exposures. The NO_2/O_3 and PAN/O_3 exposures induced significant ($p < 0.05$) decrements in $FEV_{1.0}$ compared to the FA, PAN, and NO_2 exposures in the older subject group, but at $p < 0.01$ there were no significant changes in $FEV_{1.0}$ with any exposure mixture. The older subjects had significant ($p < 0.05$) decrements in FVC with the NO_2/O_3 and $PAN/NO_2/O_3$ exposures compared to the responses to the four exposures which did not contain O_3. However, when evaluated at $p < 0.01$, there was a significant decrement in FVC only following the NO_2/O_3 exposure.

Young subjects, in contrast to the older group, had significantly ($p < 0.01$) greater changes in pulmonary function when they were exposed to O_3 and O_3-containing mixtures. There were no changes in any measure of pulmonary function with FA, PAN, NO_2 and PAN/NO_2 exposure. All four O_3-containing exposures induced significant ($p < 0.01$) decrements in FVC, $FEV_{1.0}$ and FEF25-75%. There was a significant ($p < 0.05$) post-exposure decrement in $FEV_{3.0}$ for all four O_3-containing exposures.

When the changes in $FEV_{3.0}$ were evaluated at $p < 0.01$, however, there were significant decrements following all four O_3-containing exposures compared to FA, PAN and PAN/NO_2 exposure, and following the O_3, NO_2/O_3 and $PAN/NO_2/O_3$ exposures compared to following the NO_2 exposure. The pre- to post-exposure changes in FEF75% were significantly ($p < 0.01$) greater following exposure to O_3 and $PAN/NO_2/O_3$ than following all four exposures which did not contain O_3. There were no significant changes ($p < 0.05$) in FRC, RV or ERV for any subject group or exposure condition.

2^5 ANALYSIS

The results of the 2^5 analysis of FVC, $FEV_{1.0}$ and FEF25-75% revealed no information beyond that obtained from the repeated measures analysis. The analysis of variance tables for the 2^5 analysis are included in Appendix A. The only factor or interaction that was significant was age ($p < 0.005$, 0.001, and 0.0004 respectively for FVC, $FEV_{1.0}$, and FEF25-75%). These results indicate that only O_3 exposure had any significant ($p < 0.05$) effect on pulmonary function, and that the older subjects had smaller responses than the young subjects to the exposures including O_3.

METABOLIC ANALYSIS

Male subjects, on the average, had higher $\dot{V}_E$ and lower heart rates than female subjects (Tables 8 and 9). The older subjects had lower heart rates than the younger subjects. There was no age effect on $\dot{V}_E$. There was an exposure-time period

Table 3. Mean percent change in FVC from pre- to post-exposure

	SEX				SEX		ALL		
	FEMALE		MALE						
	AGE				FEMALE	MALE	AGE		ALL
	OLD	YOUNG	OLD	YOUNG	ALL	ALL	OLD	YOUNG	ALL
EXPLEVEL									
FA	- 2.575	- 0.049	- 0.519	- 1.090	- 1.312	- 0.804	- 1.547	- 0.569	- 1.058
NO_2	- 2.638	2.345	- 0.916	0.174	- 0.146	- 0.371	- 1.777	1.260	- 0.259
O_3	7.130	10.273	3.485	17.985	8.701	10.735	5.308	14.129	9.718
O_3 + NO_2	8.086	13.182	6.562	20.511	10.634	13.537	7.324	16.847	12.085
O_3 + PAN	4.745	13.875	3.700	20.449	9.310	12.074	4.223	17.162	10.692
O_3 + PAN+ NO_2	6.126	14.616	6.634	18.207	10.371	12.421	6.380	16.412	11.396
PAN	- 0.956	1.091	- 1.600	0.219	0.067	- 0.690	- 1.278	0.655	- 0.311
PAN+ NO_2	- 1.554	1.222	- 1.103	- 2.558	- 0.166	- 1.831	- 1.328	- 0.668	- 0.998
ALL	2.296	7.070	2.030	9.237	4.683	5.634	2.163	8.153	5.158

Table 3. (continued) Mean percent change in FVC from pre- to post-exposure

STDERR

	SEX				SEX		ALL		
	FEMALE		MALE						
	AGE				FEMALE	MALE	AGE		ALL
	OLD	YOUNG	OLD	YOUNG	ALL	ALL	OLD	YOUNG	ALL
EXPLEVEL									
FA	2.116	1.168	0.952	1.287	1.212	0.777	1.152	0.850	0.710
NO_2	1.528	1.399	1.155	0.818	1.190	0.698	0.951	0.832	0.679
O_3	2.097	2.769	1.418	6.004	1.726	3.519	1.310	3.345	1.937
O_3 + NO_2	4.092	2.361	2.506	6.485	2.375	3.810	2.326	3.465	2.224
O_3 + PAN	3.093	3.382	1.946	6.080	2.508	3.766	1.770	3.466	2.239
O_3 + PAN+ NO_2	2.804	2.924	2.326	6.819	2.243	3.787	1.761	3.614	2.173
PAN	1.261	0.985	0.919	0.761	0.817	0.622	0.758	0.612	0.510
PAN+ NO_2	1.466	1.246	1.674	2.373	0.996	1.415	1.076	1.383	0.864
ALL	0.991	1.061	0.702	1.997	0.753	1.102	0.605	1.130	0.667

α = 0.01

Old: FA, NO_2, PAN, PAN/NO_2 < NO_2/O_3

Young: FA, NO_2, PAN, PAN/NO_2 < O_3, PAN/O_3, NO_2/O_3, PAN/NO_2/O_3

Old response < young response for all four O_3 exposures

Table 4. Mean percent change in $FEV_{1.0}$ from pre- to post-exposure

MEAN OF FEV1

	SEX								
	FEMALE		MALE		SEX		ALL		
	AGE				FEMALE	MALE	AGE		ALL
	OLD	YOUNG	OLD	YOUNG	ALL	ALL	OLD	YOUNG	ALL
EXPLEVEL									
FA	- 3.007	0.488	0.216	2.728	- 1.259	1.472	- 1.395	1.608	0.106
NO_2	0.258	2.227	- 0.359	1.209	1.243	0.425	- 0.050	1.718	0.834
O_3	7.052	14.715	4.152	23.685	10.883	13.919	5.602	19.200	12.401
$O_3 + NO_2$	8.566	16.228	8.241	26.807	12.397	17.524	8.404	21.517	14.961
$O_3 + PAN$	6.822	19.149	9.867	25.633	12.985	17.750	8.344	22.391	15.368
$O_3 + PAN + NO_2$	4.576	17.440	4.150	24.748	11.008	14.449	4.363	21.094	12.729
PAN	0.254	0.624	- 1.674	2.273	0.439	0.300	- 0.710	1.449	0.369
$PAN + NO_2$	0.596	1.292	0.178	- 1.830	0.944	- 0.826	0.387	- 0.269	0.059
ALL	3.140	9.020	3.087	13.157	6.080	8.127	3.118	11.089	7.103

Table 4. (continued) Mean percent change in $FEV_{1.0}$ from pre- to post-exposure

STDERR OF FEV1

	SEX								
	FEMALE		MALE		SEX		ALL		
	AGE				FEMALE	MALE	AGE		ALL
	OLD	YOUNG	OLD	YOUNG	ALL	ALL	OLD	YOUNG	ALL
EXPLEVEL									
FA	3.144	1.251	0.966	2.615	1.696	1.385	1.642	1.430	1.105
NO_2	2.039	1.429	1.124	0.500	1.230	0.628	1.128	0.743	0.683
O_3	1.759	3.916	1.975	6.468	2.298	4.127	1.331	3.831	2.339
$O_3 + NO_2$	4.017	2.908	2.014	6.357	2.591	4.015	2.171	3.643	2.395
$O_3 + PAN$	2.566	3.543	5.907	6.964	2.645	4.858	3.136	3.866	2.754
$O_3 + PAN + NO_2$	4.731	4.085	2.822	7.251	3.446	4.604	2.662	4.130	2.846
PAN	1.334	1.416	1.009	1.605	0.941	1.048	0.845	1.056	0.693
$PAN + NO_2$	1.740	0.861	1.425	0.797	0.942	0.830	1.088	0.696	0.638
ALL	1.083	1.353	1.014	2.244	0.902	1.305	0.739	1.318	0.794

$\alpha = 0.01$

Old: NS

Young: FA, PAN, NO_2, PAN/NO_2 < O_3, PAN/O_3, NO_2/O_3, $PAN/NO_2/O_3$

Old response < young response for all four O_3 exposures

Table 5. Mean percent change in $FEV_{3.0}$ from pre- to post-exposure

MEAN OF FEV3

	SEX				SEX		ALL		
	FEMALE		MALE						
	AGE				FEMALE	MALE	AGE		ALL
	OLD	YOUNG	OLD	YOUNG	ALL	ALL	OLD	YOUNG	ALL
EXPLEVEL									
FA	- 1.828	1.157	- 0.423	- 2.175	- 0.335	- 1.299	- 1.125	- 0.509	- 0.817
NO_2	- 2.075	8.115	- 1.972	4.954	3.020	1.491	- 2.024	6.535	2.256
O_3	6.664	19.508	2.754	18.909	13.086	10.832	4.709	19.209	11.959
O_3 + NO_2	8.102	17.517	7.032	21.911	12.809	14.471	7.567	19.714	13.640
O_3 + PAN	5.539	15.033	4.825	21.045	10.286	12.935	5.182	18.039	11.610
O_3 + PAN+ NO_2	5.679	14.969	7.081	23.023	10.324	15.052	6.380	18.996	12.688
PAN	- 0.588	2.310	- 1.493	7.247	0.861	2.877	- 1.041	4.778	1.869
PAN+ NO_2	- 0.895	6.285	- 0.918	0.550	2.695	- 0.184	- 0.906	3.417	1.256
ALL	2.575	10.612	2.111	11.933	6.593	7.022	2.343	11.272	6.807

Table 5. (continued) Mean percent change in $FEV_{3.0}$ from pre- to post-exposure

STDERR OF FEV3

	SEX				SEX		ALL		
	FEMALE		MALE						
	AGE				FEMALE	MALE	AGE		ALL
	OLD	YOUNG	OLD	YOUNG	ALL	ALL	OLD	YOUNG	ALL
EXPLEVEL									
FA	1.862	1.571	0.946	1.307	1.238	0.812	1.025	1.077	0.733
NO_2	1.186	5.079	1.343	5.473	2.842	2.865	0.866	3.629	1.990
O_3	1.496	7.381	1.543	6.240	3.998	3.740	1.154	4.669	2.701
O_3 + NO_2	4.050	5.308	2.386	6.776	3.447	3.966	2.275	4.196	2.589
O_3 + PAN	2.657	3.941	2.488	6.916	2.603	4.122	1.761	3.922	2.410
O_3 + PAN+ NO_2	2.681	2.822	2.287	7.314	2.230	4.235	1.712	3.927	2.392
PAN	1.275	2.480	0.700	7.007	1.398	3.584	0.712	3.647	1.901
PAN+ NO_2	1.422	5.872	1.338	3.866	3.062	1.985	0.943	3.476	1.813
ALL	0.911	1.767	0.736	2.326	1.053	1.291	0.584	1.456	0.831

α = 0.01

Old: NS

Young: FA, PAN, PAN/NO_2 < O_3, PAN/O_3, NO_2/O_3, PAN/NO_2/O_3, NO_2 < O_3, NO_2/O_3, PAN/NO_2/O_3

Old response < young response for all four O_3 exposures

Table 6. Mean percent change in FEF25-75% pre- to post-exposure

MEAN OF FEF25-75%

	SEX				SEX		ALL		ALL
	FEMALE		MALE		FEMALE	MALE	AGE		ALL
	AGE								
	OLD	YOUNG	OLD	YOUNG	ALL	ALL	OLD	YOUNG	ALL
EXPLEVEL									
FA	- 5.379	2.484	0.778	3.574	- 1.447	2.176	- 2.301	3.029	0.364
NO_2	3.347	5.665	0.560	2.709	4.506	1.634	1.953	4.187	3.070
O_3	2.817	20.570	4.006	34.676	11.693	19.341	3.411	27.623	15.517
O_3 + NO_2	12.618	22.636	11.370	36.986	17.627	24.178	11.994	29.811	20.902
O_3 + PAN	7.238	24.410	14.520	32.675	15.824	23.598	10.879	28.543	19.711
O_3 + PAN+ NO_2	12.238	25.028	6.904	32.735	18.633	19.820	9.571	28.881	19.226
PAN	0.748	2.680	- 3.617	7.463	1.714	1.923	- 1.434	5.071	1.818
PAN+ NO_2	10.273	- 0.071	1.001	- 3.317	5.101	- 1.158	5.637	- 1.694	1.971
ALL	5.487	12.925	4.440	18.438	9.206	11.439	4.964	15.681	10.323

Table 6. (continued) Mean percent change in FEF25-75% pre- to post-exposure

STDERR OF FEF25-75%

	SEX				SEX		ALL		ALL
	FEMALE		MALE		FEMALE	MALE	AGE		ALL
	AGE								
	OLD	YOUNG	OLD	YOUNG	ALL	ALL	OLD	YOUNG	ALL
EXPLEVEL									
FA	6.640	2.137	3.256	3.749	3.519	2.426	3.660	2.089	2.127
NO_2	6.487	3.761	2.388	2.297	3.634	1.624	3.358	2.162	1.975
O_3	7.153	7.054	6.022	6.696	5.367	5.882	4.519	5.039	3.976
O_3 + NO_2	5.406	4.546	3.392	6.266	3.649	4.773	3.087	4.173	3.013
O_3 + PAN	3.308	4.945	7.509	7.503	3.630	5.638	4.073	4.470	3.371
O_3 + PAN+ NO_2	6.989	6.218	6.462	8.155	4.811	6.032	4.649	5.053	3.797
PAN	4.671	3.120	2.119	4.979	2.725	2.980	2.541	2.905	1.986
PAN+ NO_2	4.989	3.238	4.838	1.643	3.168	2.530	3.564	1.803	2.072
ALL	2.083	2.029	1.777	2.765	1.485	1.751	1.364	1.725	1.148

α = 0.01

Old: NS

Young: FA, PAN, NO_2, PAN/NO_2 < O_3, PAN/O_3, NO_2/O_3, PAN/NO_2/O_3

Old response < young response for all four O_3 exposures

Table 7. Mean percent change in FEF75% pre- to post-exposure

MEAN OF FLOW75

	SEX				SEX		ALL		
	FEMALE		MALE						
	AGE				FEMALE	MALE	AGE		ALL
	OLD	YOUNG	OLD	YOUNG	ALL	ALL	OLD	YOUNG	ALL
EXPLEVEL									
FA	- 7.368	- 2.874	- 4.414	- 8.774	- 5.121	- 6.594	- 5.891	- 5.824	- 5.857
NO_2	4.235	- 6.391	- 6.134	- 5.457	- 1.078	- 5.796	- 0.950	- 5.924	- 3.437
O_3	3.985	17.058	- 5.035	37.961	10.522	16.463	- 0.525	27.510	13.492
O_3 + NO_2	-12.170	20.822	14.367	26.211	4.326	20.289	1.098	23.517	12.308
O_3 + PAN	6.623	21.990	24.572	13.683	14.307	19.127	15.598	17.837	16.717
O_3 + PAN+ NO_2	26.130	29.643	12.368	23.007	27.887	17.688	19.249	26.325	22.787
PAN	6.297	3.083	3.604	5.200	4.695	4.402	4.950	4.146	4.548
PAN+ NO_2	5.946	4.979	15.776	-16.030	5.463	- 0.128	10.861	- 5.527	2.667
ALL	4.210	11.040	6.888	9.475	7.625	8.181	5.549	10.258	7.903

Table 7. (continued) Mean percent change in FEF75% pre- to post-exposure

STDERR OF FLOW75

	SEX				SEX		ALL		
	FEMALE		MALE						
	AGE				FEMALE	MALE	AGE		ALL
	OLD	YOUNG	OLD	YOUNG	ALL	ALL	OLD	YOUNG	ALL
EXPLEVEL									
FA	8.134	5.769	8.755	6.211	4.852	5.216	5.785	4.165	3.506
NO_2	7.804	8.687	3.225	7.806	5.805	4.081	4.293	5.643	3.516
O_3	10.954	5.708	9.803	6.941	6.201	8.030	7.196	5.111	5.019
O_3 + NO_2	15.193	7.559	7.431	6.991	9.238	5.160	8.859	5.022	5.398
O_3 + PAN	6.098	6.518	6.279	17.347	4.746	9.022	4.821	9.016	5.033
O_3 + PAN+ NO_2	8.991	8.334	5.598	17.073	5.939	8.787	5.416	9.217	5.296
PAN	12.524	4.689	8.450	7.496	6.473	5.460	7.306	4.279	4.165
PAN+ NO_2	7.557	4.115	8.323	7.965	4.158	6.916	5.577	5.110	4.001
ALL	3.609	2.688	2.844	4.197	2.261	2.528	2.292	2.483	1.693

α = 0.01

Old: NS

Young: FA, NO_2, PAN/NO_2 < O_3, PAN/NO_2/O_3

Old response < young response for all four O_3 exposures

interaction ($p < 0.05$) for heart rate, in that heart rate tended to decrease with time during the four O_3 exposures, while there was little difference in the mean heart rates across the three exercise periods of the four non-O_3 exposures.

SYMPTOM ANALYSIS

The number of subjects reporting symptoms commonly associated with exercise and air pollutant exposure is given by sex and age group in Table 10. Tables of specific symptoms with the number of subjects reporting each are in Appendix B.

The four subject groups had similar symptomatology for the FA, PAN, NO_2 and PAN/NO_2 exposures. All four subject groups reported an increased number of symptoms following exposure to O_3 and the three O_3-containing mixtures than following the FA, PAN, NO_2 and PAN/NO_2 exposures. Except for the older women, more symptoms were reported following exposure to mixtures including O_3 than following exposure to O_3 alone.

Table 8A. Mean minute ventilation rate by exercise period for the eight exposures

MEAN OF VBTPS

		SEX						ALL		
		FEMALE		MALE		SEX		AGE		ALL
		AGE				FEMALE	MALE			
		OLD	YOUNG	OLD	YOUNG	ALL	ALL	OLD	YOUNG	ALL
EXP LEVEL	PERIOD									
FA	1	25.513	20.421	27.780	27.356	23.117	27.582	26.580	23.657	25.210
	2	26.626	21.826	27.786	27.887	24.367	27.833	27.172	24.655	25.992
	3	25.009	23.089	29.122	26.917	24.105	28.093	26.945	24.875	25.975
NO_2	1	26.418	23.349	26.346	28.026	24.974	27.130	26.384	25.531	25.984
	2	26.751	23.842	27.219	27.976	25.382	27.572	26.971	25.771	26.409
	3	25.537	23.581	24.812	27.634	24.616	26.129	25.196	25.473	25.326
O_3	1	24.610	22.114	27.747	24.786	23.435	26.365	26.086	23.361	24.809
	2	25.348	22.527	28.136	27.106	24.021	27.655	26.660	24.664	25.724
	3	26.189	22.127	27.744	23.656	24.278	25.836	26.921	22.841	25.008
O_3 + NO_2	1	24.507	22.439	28.152	24.480	23.534	26.439	26.222	23.391	24.895
	2	25.408	22.591	28.911	25.769	24.082	27.445	27.056	24.074	25.658
	3	26.533	22.397	27.414	27.651	24.587	27.525	26.948	24.849	25.964
O_3 + PAN	1	27.984	20.799	26.896	27.143	24.603	27.011	27.472	23.759	25.732
	2	24.647	21.199	29.756	28.361	23.024	29.105	27.051	24.541	25.875
	3	24.438	21.490	25.585	27.223	23.051	26.349	24.978	24.165	24.597
O_3 + PAN+ NO_2	1	26.778	21.326	30.200	29.451	24.212	29.851	28.388	25.118	26.855
	2	25.488	21.984	27.814	28.641	23.839	28.200	26.582	25.091	25.883
	3	23.708	21.856	27.397	26.547	22.836	27.001	25.444	24.045	24.788
PAN	1	26.088	22.080	27.936	29.673	24.202	28.747	26.958	25.623	26.332
	2	24.543	22.835	25.917	30.101	23.739	27.870	25.190	26.226	25.676
	3	25.280	22.339	26.877	28.864	23.896	27.805	26.032	25.384	25.728
PAN+ NO_2	1	24.641	23.999	27.305	29.309	24.339	28.240	25.895	26.477	26.167
	2	23.628	23.640	28.561	28.147	23.634	28.368	25.949	25.743	25.853
	3	25.506	23.707	29.801	27.096	24.659	28.539	27.527	25.289	26.478

$\alpha = 0.01$

Men > women

No effects by any pollutant(s)

Table 8B. Standard error of the ventilation rate by exercise period for the eight exposures

STDERR OF VBTPS

	SEX				SEX		ALL		
	FEMALE		MALE						
	AGE				FEMALE	MALE	AGE		ALL
	OLD	YOUNG	OLD	YOUNG	ALL	ALL	OLD	YOUNG	ALL
EXPLEVEL									
FA	2.025	0.962	2.657	1.816	1.296	1.595	1.619	1.327	1.077
FA	1.654	0.999	2.427	1.372	1.135	1.395	1.399	1.138	0.980
FA	2.125	1.181	3.550	1.233	1.241	1.937	2.013	0.968	1.159
NO_2	2.245	0.988	1.124	2.024	1.297	1.098	1.263	1.212	0.868
NO_2	1.886	1.662	2.437	2.108	1.281	1.575	1.472	1.389	1.007
NO_2	1.671	1.426	3.070	1.739	1.103	1.805	1.639	1.200	1.021
O_3	1.473	1.177	0.997	1.552	0.978	0.950	0.966	0.989	0.723
O_3	1.421	1.577	0.978	1.453	1.082	0.834	0.923	1.208	0.708
O_3	1.279	1.141	1.142	1.422	0.979	1.024	0.860	0.891	0.710
O_3 + NO_2	1.259	0.932	1.557	1.405	0.816	1.132	1.061	0.837	0.722
O_3 + NO_2	1.585	1.608	1.569	2.005	1.149	1.279	1.167	1.293	0.894
O_3 + NO_2	1.361	1.226	1.435	2.222	1.032	1.240	0.962	1.371	0.829
O_3 + PAN	2.306	0.951	2.096	1.617	1.549	1.302	1.527	1.216	1.031
O_3 + PAN	1.194	0.689	1.660	1.549	0.813	1.118	1.162	1.232	0.862
O_3 + PAN	2.053	0.952	2.543	1.887	1.199	1.576	1.571	1.240	1.004
O_3 + PAN + NO_2	1.619	0.967	2.580	3.054	1.162	1.911	1.499	1.813	1.182
O_3 + PAN + NO_2	1.623	1.025	1.716	2.793	1.051	1.535	1.178	1.621	0.977
O_3 + PAN + NO_2	1.941	0.948	1.968	2.815	1.112	1.622	1.417	1.488	1.017
PAN	1.179	0.882	1.516	3.427	0.882	1.736	0.946	1.892	1.008
PAN	1.818	1.323	1.116	2.137	1.132	1.248	1.078	1.523	0.904
PAN	2.297	1.121	1.658	2.127	1.338	1.307	1.415	1.413	0.987
PAN + NO_2	1.328	1.754	1.626	3.142	1.052	1.659	1.059	1.816	1.004
PAN + NO_2	1.065	1.255	2.405	1.941	0.790	1.516	1.368	1.239	0.916
PAN + NO_2	0.633	1.235	3.076	1.867	0.686	1.830	1.530	1.144	0.979

Table 9A. Mean heart rate by exercise period for the eight exposures

MEAN OF FC

		SEX				SEX		ALL		
		FEMALE		MALE				AGE		ALL
		AGE				FEMALE	MALE			
		OLD	YOUNG	OLD	YOUNG	ALL	ALL	OLD	YOUNG	ALL
EXP LEVEL	PERIOD									
FA	1	109.78	112.38	86.750	102.57	111	94.133	98.941	107.8	103.09
	2	112.56	113.25	87.375	102	112.88	94.200	100.71	108	104.13
	3	113.22	116.38	86.750	103.14	114.71	94.400	100.76	110.2	105.19
NO_2	1	111.33	124.5	84.000	102.14	117.53	92.467	98.471	114.07	105.78
	2	113.78	121	83.375	99.571	117.18	90.933	99.471	111	104.88
	3	113.67	122.88	83.000	98.143	118	90.067	99.235	111.33	104.91
O_3	1	111	112.63	85.250	103.43	111.76	93.733	98.882	108.33	103.31
	2	109	113.63	85.250	99.000	111.18	91.667	97.824	106.8	102.03
	3	108.56	115.13	84.375	96.571	111.65	90.067	97.176	106.47	101.53
O_3 + NO_2	1	115.33	121.5	88.375	103.43	118.24	95.400	102.65	113.07	107.53
	2	111.44	120	88.250	97.571	115.47	92.600	100.53	109.53	104.75
	3	108.11	121.13	86.750	96.714	114.24	91.400	98.059	109.73	103.53
O_3 + PAN	1	114.33	123.38	89.250	102	118.59	95.200	102.53	113.4	107.63
	2	112.11	122	84.500	100	116.76	91.733	99.118	111.73	105.03
	3	110.89	121	78.750	98.857	115.65	88.133	95.765	110.67	102.75
O_3 + PAN+ NO_2	1	113.22	122.75	89.875	102.29	117.71	95.667	102.24	113.2	107.38
	2	110.67	120.13	88.750	100.43	115.12	94.200	100.35	110.93	105.31
	3	108.56	119	87.000	97.143	113.47	91.733	98.412	108.8	103.28
PAN	1	110.33	119.38	85.375	110.43	114.59	97.067	98.588	115.2	106.38
	2	110.22	119	85.875	110.71	114.35	97.467	98.765	115.13	106.44
	3	109.44	118.88	84.000	109.57	113.88	95.933	97.471	114.53	105.47
PAN+ NO_2	1	111.78	120.88	85.750	101.14	116.06	92.933	99.529	111.67	105.22
	2	112.78	122.25	83.375	102.14	117.24	92.133	98.941	112.87	105.47
	3	114	121.75	84.625	103.29	117.65	93.333	100.18	113.13	106.25

α = 0.01

Men < women

Old < young

Exposure/period interaction

Table 9B. Standard error of the mean heart rate by exercise period for the eight exposures

STDERR OF FC

		SEX								
		FEMALE		MALE		SEX		ALL		
		AGE				FEMALE	MALE	AGE		ALL
		OLD	YOUNG	OLD	YOUNG	ALL	ALL	OLD	YOUNG	ALL
EXP LEVEL	PER-IOD									
FA	1	3.407	2.777	3.736	4.820	2.183	3.580	3.769	2.900	2.511
	2	3.037	2.534	3.396	5.224	1.942	3.512	3.833	3.069	2.540
	3	3.394	2.500	3.634	6.288	2.119	4.026	4.084	3.562	2.824
NO_2	1	4.041	2.528	4.009	5.869	2.888	4.126	4.389	4.181	3.307
	2	3.589	2.570	4.204	4.755	2.363	3.728	4.631	3.801	3.163
	3	4.537	2.371	4.013	5.360	2.815	3.757	4.838	4.257	3.381
O_3	1	2.906	2.405	3.589	3.841	1.862	3.502	3.900	2.449	2.482
	2	2.713	2.909	4.126	4.567	2.006	3.475	3.773	3.199	2.592
	3	3.132	3.330	4.035	4.225	2.356	3.249	3.880	3.556	2.738
O_3 + NO_2	1	4.500	3.105	3.246	3.963	2.817	3.159	4.341	3.394	2.912
	2	2.839	3.012	3.385	3.373	2.267	2.622	3.587	3.693	2.658
	3	3.518	2.924	3.683	4.597	2.770	3.100	3.629	4.135	2.886
O_3 + PAN	1	3.812	3.669	5.769	3.910	2.809	3.850	4.527	3.843	3.114
	2	4.794	2.353	4.496	4.180	2.957	3.627	4.703	3.685	3.196
	3	6.213	3.262	3.081	4.323	3.742	3.668	5.315	3.911	3.573
O_3 + PAN+ NO_2	1	3.778	2.858	3.782	4.789	2.622	3.338	3.900	3.770	2.854
	2	4.859	2.401	3.604	5.690	2.972	3.516	4.050	3.861	2.925
	3	5.276	3.354	3.901	6.577	3.374	3.813	4.211	4.488	3.161
PAN	1	4.311	1.792	1.499	3.294	2.618	3.732	3.883	2.109	2.701
	2	4.570	1.783	2.232	4.075	2.717	3.952	3.973	2.321	2.761
	3	3.881	1.517	2.130	4.705	2.418	4.155	3.873	2.565	2.801
PAN+ NO_2	1	3.349	2.985	4.288	5.244	2.468	3.823	4.160	3.847	3.010
	2	3.312	2.374	3.545	6.193	2.337	4.157	4.353	4.045	3.197
	3	3.640	2.484	4.204	6.179	2.390	4.306	4.537	3.917	3.200

Table 10. Total number of reported symptoms by age and sex for the eight exposures (summary)

Group	FA	PAN	O_3	NO_2	PAN/O_3	PAN/NO_2	NO_2/O_3	PAN/NO_2/O_3
Young men	18	22	44	14	57	31	57	58
Young women	18	26	29	28	44	31	51	48
Older men	14	29	38	19	47	29	39	55
Older women	10	20	40	12	39	23	32	39
Men	32	51	82	33	104	60	96	113
Women	28	46	69	40	83	54	83	87

Table 11. Statistical significance of those symptoms which were not uniformly reported across the eight exposures

	Unusual Odor	Cough	Shortness of breath	Chest Tightness	Eye Irritation
All subjects	0.02	0.001	0.01	0.001	0.05
Young subjects	0.001	0.001	0.001	0.001	0.05
Older subjects	0.05	0.02	NS	NS	0.10

Of the 16 symptoms listed on the symptom questionnaire (see Appendix B for list), the Cochran Q test found that the frequency of "yes" responses across the eight exposures was significantly different for five symptoms: unusual odor, cough, shortness of breath, chest tightness, and eye irritation. Table 11 presents the statistical significance levels for these five symptoms for all subjects together (n = 32), and divided by age (i.e. 16 young/16 old). The analysis indicates that the increased number of reports of eye irritation can be related to inclusion of PAN in the exposure condition. The increased number of reports of unusual odor, cough, shortness of breath and chest tightness occurred when O_3 was included in the exposure.

There were obvious differences between the responses of the older and younger subjects on several of the symptoms. Shortness of breath and chest tightness were frequently reported by young subjects following exposures including O_3. There were, however, no significant ($p > 0.05$) differences among the older subjects' reports of shortness of breath and chest tightness among the eight exposures. While eye irritation was not reported uniformly across all eight exposures, when all 32 subjects were included, the analysis indicates that the finding of statistical significance is primarily due to an increase in reports of eye irritation by the young subjects following exposures including PAN. Differences in reports of eye irritation by the older subjects only approached significance.

DISCUSSION

A major aim of this study was to investigate whether or not there were significant interactions between PAN, NO_2, and O_3. The lack of significant responses following exposure to FA, PAN, NO_2, and PAN/NO_2 was anticipated and is in agreement with earlier reports (Drechsler-Parks et al., 1984; Folinsbee et al., 1978; Gliner at el., 1975; Horvath et al., 1978, 1986; Raven et al., 1974a, 1974b, 1976). Ozone exposure, however, induced significant decrements in pulmonary function, in agreement with earlier reports (Bates et al., 1972; Folinsbee et al., 1978a; Hazucha et al., 1973; Young et al., 1964). The changes in pulmonary function with PAN/O_3, NO_2/O_3, and PAN/NO_2/O_3 exposure were not significantly ($p > 0.05$) different from the changes which occurred following exposure to O_3 alone, the results with NO_2/O_3 exposure being in agreement with earlier reports (Folinsbee et al., 1981; Hackney et al., 1975a, 1975b; Horvath et al., 1979). However, there was a trend toward slightly larger decrements in pulmonary function following exposure to the three mixtures containing O_3 compared to exposure to O_3 alone. But, even if these slightly larger decrements following exposure to the O_3 mixtures had been significantly larger statistically than those following exposure to O_3 alone, the small size of the differences observed would make them of doubtful clinical or functional significance. Since including PAN and/or NO_2 with O_3 in the exposure mixture had no additional effect beyond that of exposure to O_3 alone, the results suggest that O_3 is responsible for the changes observed in pulmonary function.

Our earlier studies (Drechsler-Parks et al., 1984; Horvath et al., 1986) comparing the effects of O_3 and PAN/O_3 exposure found, on the average, 10% greater decrements in pulmonary function with PAN/O_3 exposure than with exposure to O_3 alone. Exposure to PAN alone had no significant effects ($p > 0.05$). The non-significant ($p > 0.05$) interaction between PAN and O_3 in the present study may be due to the lower PAN concentration (0.13 ppm) used here compared to that of the earlier study (0.30 ppm). If the interaction observed in the earlier investigation is a linear function, the increase in decrements following exposure to 0.13 ppm PAN plus 0.45 ppm O_3 would be expected to be less than 5%, since a 10% increase in decrements was observed when 0.30 ppm PAN was added to 0.45 ppm O_3. A change of less than 5% would be within the error range of the pulmonary function measurements, and would not be statistically evident.

Another purpose of this study was to compare the responses of men and women to exposure to O_3, and to various mixtures of O_3, NO_2 and PAN. Since there were no statistically significant ($p > 0.05$) differences between the O_3 and O_3-containing mixture exposures, we will use "O_3" to refer to all exposures containing O_3, whether alone or in mixtures, for this section of the discussion. The lack of significant ($p > 0.05$) differences between the responses of men and women for any pulmonary function measured suggests, on superficial analysis, that there is no difference between the responses of men and women to O_3 or to mixtures of O_3 and NO_2 and/or PAN.

At present, there is considerable uncertainty in comparing the responses to air pollutants of men and women. It is presently unknown if, or how, the data should be normalized. When compared on an absolute volume basis, men tend to have larger decrements in pulmonary function following O_3 exposure

than women. However, men generally have a larger total lung volume than women, so that an equal volume change is a larger fraction (percentage) of the total lung volume of women than men. When compared on a percentage decrement basis, women tend to have similar to larger decrements than men in response to exposure to equal effective doses of O_3, with some variability related to individual responsiveness (Gibbons et al., 1984; Lategola et al., 1980). Several reports have found no difference between men and women (Gliner et al., 1983; Horvath et al., 1986; Linn et al., 1980).

A number of methods for normalizing the effective doses of O_3 inhaled by men and women have been suggested. Among them are to have men and women exercise at equal percentages of $\dot{V}_{O2}$ max; however, Lauritzen et al., 1985, found that their women subjects still had larger decrements than men subjects. Other methods which have been suggested include having men and women exercise at equal percentages of $\dot{V}_{E\ max}$, matching the ratio of alveolar surface area to body weight, and matching respiratory frequency (Lauritzen et al., 1985). None of these methods, however, has been validated, and none appears to fully explain the difference noted between the responses of men and women. In light of the existing uncertainties, we believe that the most appropriate comparison is the percentage change in pulmonary function from pre- to post-exposure, since this removes at least part of the influence of lung size differences between men and women.

Previous research (Folinsbee et al., 1978a; Silverman et al., 1976) has indicated that pulmonary function responses to O_3 exposure are related to the "effective dose" of O_3 to which the subject is exposed. Effective dose is defined as the simple product of O_3 concentration (in ppm), mean $\dot{V}_E$ for the exposure period (in L/min) and time of exposure (in min). Although the range of individual responses to O_3 is very wide, the general rule is that as the effective dose of O_3 increases, the magnitude of the pulmonary function responses also increases.

We attempted to have all subjects inhale the same effective dose of O_3 by having all subjects exercise at a work load which induced a $\dot{V}_E$ of 25 L/min. However, the results indicate that the men had a higher ($p < 0.007$) mean exercise ventilation rate (27.2 L/min) than the women (24.0 L/min). Women have lower resting ventilation rates than men, as well. The estimated effective doses of O_3 for our subjects were 9.50×10^{-4} L for the men, and 8.37×10^{-4} for the women (Folinsbee et al., 1978a). The older women had somewhat larger ($p < 0.05$) mean changes in $FEV_{1.0}$ than the older men. The young women had a mean change in $FEV_{1.0}$ smaller, though not statistically ($p > 0.05$) smaller, than the young men. Within each age group, the responses of the men and women covered the same range of percentage decrements, with the sole exception of one extraordinarily responsive young man whose decrement in $FEV_{1.0}$ after a 2-hour exposure to 0.45 ppm O_3 was in excess of 50%.

The reports which have compared the responses of men and women to O_3 have generally concluded that women appear to be more responsive to O_3 than men (Gibbons et al., 1984; Horvath et al., 1979, Lategola et al., 1980; Lauritzen et al., 1985). The most extensive comparison of the responses to O_3 exposure of men and women was published by Lauritzen et al., 1985. These authors studied the responses of six young women exposed for 1 hour to each of several O_3 concentrations while they performed continuous cycle ergometer exercise at each of several work loads. The women's responses were then compared to those of a group of young men previously studied at the same laboratory (Adams et al., 1981) who had followed the same protocol. The men and women were compared at the same absolute effective doses of O_3 (equal $\dot{V}_E$, O_3 concentration and time period), and at the same relative effective doses of O_3 (equal time period and O_3 concentration, $\dot{V}_{O2}$ at the same percentage of maximal). The results indicated that the women had larger mean decrements in pulmonary function following O_3 exposure than the men, regardless of whether the comparison was at the same absolute, or the same relative effective dose of O_3. While our results are not conclusive, the finding that there were no statistically significant ($p > 0.05$) differences between the percentage decrements of the men and women, indicating that the responses of men and women fell into the same range, in spite of the women inhaling less O_3 than the men, suggests that women may be somewhat more responsive to O_3 than men, in agreement with some reports (Gibbons et al., 1984; Horvath et al., 1979; Lauritzen et al., 1985; Lategola et al., 1980) and at variance with others (Gliner et al., 1983; Linn et al., 1980).

The third purpose of this study was to compare the responses to oxidant pollutants of men and women between 18-26 years of age with those of men and women over 50 years of age. The mean decrement in $FEV_{1.0}$ following exposure to 0.45 ppm O_3 was 5.6% for the older subjects and 19.2% for the younger subjects. Similar mean decrements occurred following exposure to the O_3 mixtures. Although these preliminary results suggest that older people are less responsive than younger people, there are few published data on individuals over 50 years of age available for us to compare with those of this study, although Schlenker et al., 1980, have reported in an abstract that their elderly subjects were less responsive to a mixture of 0.50 ppm SO_2 + 0.50 ppm O_3 than their young adult subjects. It should be noted that while the older subjects exhibited fewer and smaller changes in pulmonary function following exposures containing O_3 than the young subjects, the same pattern of responses occurred, though the responses were attenuated. It should also be noted that two older men and two older women had decrements in $FEV_{1.0}$ following the O_3 exposure of 10-14%, similar to the response of an "average" young adult.

There are at least two potential explanations for the minimal responsiveness of our older subject group. One possibility

is that, for the most part, minimally responsive people volunteered to participate. Another possibility is that people become less responsive as they get older. There is some suggestive support for both views. It is already well established that there is a very wide range of responsiveness among young people. The subjects in this study were all paid volunteers, and were not initially screened for responsiveness. We have previously studied groups of young men and women who were selected in the same manner, i.e. solely on the basis of being willing to participate and of having normal cardiac and pulmonary function. Such groups have varied in their mean responses. It is, therefore, possible that minimally responsive people were, by chance, the ones who happened to volunteer to participate in the older group.

There are a number of physiological changes which occur with aging, some of which could be considered suggestive of older people being either more or less responsive to oxidant pollutants than younger people. It is well established that there are reductions in pulmonary function with aging (Dockery et al., 1985; Knudson et al., 1983). Older individuals have a reduced number of cilia and their ability to move mucus is hampered, possibly leading to greater protection for airway smooth muscle and airway irritant receptors by allowing mucus to accumulate in the airways. If this occurs, older individuals may be less sensitive than younger individuals to O_3 exposure. Aging also is associated with a number of changes which result in attenuation of various physiological processes; for example, longer reaction time, slowed reflexes and diminished responses to various stressors (e.g. heat stress, Robinson et al., 1965). These changes make it conceivable that responsiveness to O_3 might be reduced with aging, in agreement with the present results. Further studies with more subjects and selection for responsiveness (greater or less) are necessary before the issue of the sensitivity of older people to O_3 exposure can be explained.

Analysis of the symptom reports indicates that relatively few of the symptoms queried were attributable to pollutant exposure. With the exception of eye irritation, attributable to PAN exposure for only the young subjects, the symptoms not uniformly reported across the eight conditions (*viz.*, unusual odor, cough, shortness of breath and chest tightness) were reported more often following exposures including O_3. The symptom reports of the older subjects, however, appear to be less specific to any pollutant or mixture than those of the young subjects. A statistically significant ($p < 0.05$) excess of positive responses was reported by the older subjects only for unusual odor and cough. Cough was primarily reported following exposures including O_3. Unusual odor was reported more frequently subsequent to exposure to O_3 and to all four pollutant mixtures. It should be noted that the older subjects reported a similar total number of symptom responses as the young subjects although they had small pulmonary function responses. This suggests that general symptom reports, except possibly for the item "cough," may not be representative of the degree of pulmonary function impairment experienced consequent to air pollutant exposure, and may in fact be more related to the intensity of exercise during the exposure, or to individual discomfort tolerance.

In conclusion, we performed a pilot study consisting of a series of exposures of men and women (18 to 26, and 51 to 76 years of age) to O_3, NO_2 and PAN alone and in various mixtures. There were several questions of interest. First, we investigated whether there were interactions between PAN, NO_2 and O_3. We found no interactions, and the results implicate O_3 as the cause of the pulmonary function changes observed. Second, we compared the responses of men and women to PAN, NO_2 and O_3. The results suggest that women may be somewhat more responsive to O_3 than men. Third, we compared the responses of older men and women (51-76 years of age) and younger men and women (18-26 years of age) to exposure to PAN, NO_2 and O_3 exposure. The results suggest that older people may be less responsive than younger people to O_3 exposure. Further investigation is required before the issues of sex and age group differences can be considered settled.

CONCLUSIONS

1. Exposure to FA, PAN, NO_2 and PAN/NO_2 had no significant effects on pulmonary function.
2. Ozone appears to be responsible for the pulmonary function effects observed.
3. Responses to mixtures of O_3 plus NO_2 and/or PAN were not different from the responses to exposure to O_3 alone, indicating that there were were no interactions among O_3, NO_2 and PAN.
4. Women may be more responsive to O_3 exposure than men.
5. Older people (51-76 years of age) may be less responsive to O_3 than younger people (18-26 years of age), though several responded similarly to an "average" young person.

RECOMMENDATIONS

1. Although more expensive and time consuming, larger groups of subjects are needed to better characterize the responses of people in general to air pollutants. Large groups are more likely to reflect the broad range of responsiveness that appears to exist among individuals. Results based on small subject groups may easily be biased if preponderantly non-responders or hyper-responders happen to volunteer to participate.

2. Further investigation should be made of the responses of older men and women to air pollutant exposure with the purpose of evaluating the range, magnitude and nature of their responses, and comparing them to those of young people.
3. The range and distribution of the responses to O_3 exposure of young men and women should be better characterized.

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APPENDIX A — ANALYSIS OF VARIANCE TABLES

TABLE A-1. BMDP2V FVC PRE POST PERCENT DIFF ANALYSIS OF HEINOP

ANALYSIS OF VARIANCE FOR 1st
DEPENDENT VARIABLE — FVCD4 FVCD8 FVCD12 FVCD16 FVCD20 FVCD24 FVCD28 FVCD32

	Source	Sum of Squares	Degrees of Freedom	Mean Square	F	Tail Probability	Greenhouse Geisser Probability	Huynh Feldt Probability
	Mean	6811.34081	1	6811.34081	27.63	0.0000		
	Sex	57.92087	1	57.92087	0.23	0.6316		
	Age	2296.60598	1	2296.60598	9.32	0.0049		
	SA	94.68644	1	94.68644	0.38	0.5404		
1	Error	6901.70666	28	246.48952				
	Exposure	8771.88961	7	1253.12709	27.69	0.0	0.0	0.0
	ES	166.51942	7	23.78849	0.53	0.8146	0.5942	0.6252
	EA	1310.70819	7	187.24403	4.14	0.0003	0.0211	0.0150
	ESA	540.49789	7	77.21398	1.71	0.1095	0.1909	0.1838
2	Error	8871.07218	196	45.26057				

Error Term Epsilon Factors For Degrees of Freedom Adjustment

	Greenhouse-Geisser	Huynh-Feldt
2	0.2858	0.3408

TABLE A-2. BMDP2V FEV1 PRE POST PERCENT DIFF ANALYSIS OF HEINOP

ANALYSIS OF VARIANCE FOR 1st

DEPENDENT VARIABLE — FEV1D4 FEV1D8 FEV1D12 FEV1D16 FEV1D20 FEV1D24 FEV1D28 FEV1D32

	Source	Sum of Squares	Degrees of Freedom	Mean Square	F	Tail Probability	Greenhouse Geisser Probability	Huynh Feldt Probability
	Mean	12916.94099	1	12916.94099	47.54	0.0000		
	Sex	268.05225	1	268.05225	0.99	0.3291		
	Age	4065.78258	1	4065.78258	14.96	0.0006		
	SA	279.44446	1	279.44446	1.03	0.3192		
1	Error	7607.46937	28	271.69533				
	Exposure	11935.49480	7	1705.07069	24.84	0.0	0.0	0.0
	ES	382.52020	7	54.64574	0.80	0.5915	0.4909	0.5138
	EA	2745.02998	7	392.14714	5.71	0.0	0.0018	0.0007
	ESA	425.85508	7	60.83644	0.89	0.5184	0.4452	0.4626
2	Error	13455.69789	196	68.65152				

Error Term Epsilon Factors For Degrees of Freedom Adjustment

	Greenhouse-Geisser	Huynh-Feldt
2	0.3954	0.4902

TABLE A-3. BMDP2V FEV3 PRE POST PERCENT DIFF ANALYSIS OF HEINOP

ANALYSIS OF VARIANCE FOR 1st
DEPENDENT VARIABLE — FEV3D4 FEV3D8 FEV3D12 FEV3D16 FEV3D20 FEV3D24 FEV3D28 FEV3D32

	Source	Sum of Squares	Degrees of Freedom	Mean Square	F	Tail Probability	Greenhouse Geisser Probability	Huynh Feldt Probability
	Mean	11863.53495	1	11863.53495	30.63	0.0000		
	Sex	11.75554	1	11.75554	0.03	0.8629		
	Age	5103.12904	1	5103.12904	13.18	0.0011		
	SA	50.97032	1	50.97032	0.13	0.7195		
1	Error	10843.71529	28	387.27555				
	Exposure	8478.12278	7	1211.16040	12.88	0.0	0.0	0.0
	ES	410.89843	7	58.69978	0.62	0.7356	0.6224	0.6611
	EA	1364.15382	7	194.87912	2.07	0.0482	0.1004	0.0821
	ESA	409.30437	7	58.47205	0.62	0.7376	0.6240	0.6628
2	Error	18433.21462	196	94.04701				

Error Term Epsilon Factors For Degrees of Freedom Adjustment

	Greenhouse-Geisser	Huynh-Feldt
2	0.4908	0.6277

TABLE A-4. BMDP2V MMEF PRE POST PERCENT DIFF ANALYSIS OF HEINOP

ANALYSIS OF VARIANCE FOR 1st

DEPENDENT VARIABLE — MMEFD4 MMEFD8 MMEFD12 MMEFD16 MMEFD20 MMEFD24 MMEFD28 MMEFD32

	Source	Sum of Squares	Degrees of Freedom	Mean Square	F	Tail Probability	Greenhouse Geisser Probability	Huynh Feldt Probability
	Mean	27278.19339	1	27278.19339	60.22	0.0000		
	Sex	319.04958	1	319.04958	0.70	0.4085		
	Age	7351.41757	1	7351.41757	16.23	0.0004		
	SA	688.44989	1	688.44989	1.52	0.2279		
1	Error	12684.03371	28	453.00120				
	Exposure	19205.17246	7	2743.59607	14.49	0.0	0.0	0.0
	ES	1471.67164	7	210.23881	1.11	0.3582	0.3570	0.3585
	EA	6392.50241	7	913.21463	4.82	0.0000	0.0007	0.0001
	ESA	765.25608	7	109.32230	0.58	0.7740	0.7016	0.7517
2	Error	37120.51995	196	189.39041				

Error Term Epsilon Factors For Degrees of Freedom Adjustment

	Greenhouse-Geisser	Huynh-Feldt
2	0.6504	0.8755

TABLE A-5. BMDP2V FLOW75 PRE POST PERCENT DIFF ANALYSIS OF HEINOP

ANALYSIS OF VARIANCE FOR 1st
DEPENDENT VARIABLE — VARD4 VARD8 VARD12 VARD16 VARD20 VARD24 VARD28 VARD32

	Source	Sum of Squares	Degrees of Freedom	Mean Square	F	Tail Probability	Greenhouse Geisser Probability	Huynh Feldt Probability
	Mean	15989.92840	1	15989.92840	15.51	0.0005		
	Sex	19.81774	1	19.81774	0.02	0.8907		
	Age	1418.93657	1	1418.93657	1.38	0.2506		
	SA	288.11124	1	288.11124	0.28	0.6012		
1	Error	28859.86491	28	1030.70946				
	Exposure	22607.17988	7	3229.59713	5.65	0.0	0.0000	0.0000
	ES	3765.23841	7	537.89120	0.94	0.4766	0.4635	0.4766
	EA	11681.58762	7	1668.79823	2.92	0.0063	0.0119	0.0063
	ESA	6237.99814	7	891.14259	1.56	0.1501	0.1680	0.1501
2	Error	112126.19732	196	572.07244				

Error Term Epsilon Factors For Degrees of Freedom Adjustment

	Greenhouse-Geisser	Huynh-Feldt
2	0.7969	1.0000

TABLE A-6. BMDP2V HEINOP 2N ANALYSIS OF FVC**

ANALYSIS OF VARIANCE FOR 1st
DEPENDENT VARIABLE — FVCP1 FVCP2 FVCP3 FVCP4 FVCP5 FVCP6 FVCP7 FVCP8

	Source	Sum of Squares	Degrees of Freedom	Mean Square	F	Tail Probability
	Mean	6811.34081	1	6811.34081	27.63	0.0000
	Age	2296.60598	1	2296.60598	9.32	0.0049
	Sex	57.92087	1	57.92087	0.23	0.6316
	AS	94.68644	1	94.68644	0.38	0.5404
1	Error	6901.70666	28	246.48952		
	O3	8655.88766	1	8655.88766	40.14	0.0000
	OA	1204.62091	1	1204.62091	5.59	0.0253
	OS	141.35438	1	141.35438	0.66	0.4250
	OAS	448.59703	1	448.59703	2.08	0.1603
2	Error	6038.64019	28	215.66572		
	NO2	40.53522	1	40.53522	2.41	0.1321
	NA	2.01604	1	2.01604	0.12	0.7320
	NS	2.20701	1	2.20701	0.13	0.7201
	NAS	35.03434	1	35.03434	2.08	0.1604
3	Error	471.80939	28	16.85034		
	ON	35.01397	1	35.01397	2.27	0.1430
	ONA	8.95377	1	8.95377	0.58	0.4523
	ONS	3.21856	1	3.21856	0.21	0.6512
	ONAS	1.25493	1	1.25493	0.08	0.7775
4	Error	431.58982	28	15.41392		
	PAN	0.34100	1	0.34100	0.03	0.8695
	PA	10.27697	1	10.27697	0.83	0.3705
	PS	7.99959	1	7.99959	0.64	0.4287
	PAS	12.17162	1	12.17162	0.98	0.3304
5	Error	347.34551	28	12.40520		
	OP	0.30835	1	0.30835	0.02	0.8915
	OPA	36.57428	1	36.57428	2.25	0.1450
	OPS	6.66740	1	6.66740	0.41	0.5273
	OPAS	36.23523	1	36.23523	2.23	0.1468
6	Error	455.65050	28	16.27323		
	NP	39.67791	1	39.67791	2.03	0.1656
	NPA	48.18895	1	48.18895	2.46	0.1279
	NPS	3.08844	1	3.08844	0.16	0.6943
	NPAS	6.86069	1	6.86069	0.35	0.5586
7	Error	548.24187	28	19.58007		
	ONP	0.12549	1	0.12549	0.01	0.9384
	ONPA	0.07727	1	0.07727	0.00	0.9516
	ONPS	1.98404	1	1.98404	0.10	0.7588
	ONPAS	0.34405	1	0.34405	0.02	0.8982
8	Error	577.79491	28	20.63553		

TABLE A-7. BMDP2V HEINOP 2N ANALYSIS OF FEV1**

ANALYSIS OF VARIANCE FOR 1st
DEPENDENT VARIABLE — FEV1P1 FEV1P2 FEV1P3 FEV1P4 FEV1P5 FEV1P6 FEV1P7 FEV1P8

	Source	Sum of Squares	Degrees of Freedom	Mean Square	F	Tail Probability
	Mean	12630.08403	1	12630.08403	43.48	0.0000
	Age	3905.55191	1	3905.55191	13.45	0.0010
	Sex	228.10746	1	228.10746	0.79	0.3831
	AS	238.62581	1	238.62581	0.82	0.3725
1	Error	8132.84436	28	290.45873		
	O3	11429.83931	1	11429.83931	42.02	0.0000
	OA	2494.65366	1	2494.65366	9.17	0.0052
	OS	227.83362	1	227.83362	0.84	0.3679
	OAS	254.72870	1	254.72870	0.94	0.3415
2	Error	7616.50715	28	272.01811		
	NO2	3.78133	1	3.78133	0.09	0.7633
	NA	0.33799	1	0.33799	0.01	0.9282
	NS	9.87828	1	9.87828	0.24	0.6268
	NAS	0.00672	1	0.00672	0.00	0.9899
3	Error	1144.57810	28	40.87779		
	ON	0.07589	1	0.07589	0.00	0.9687
	ONA	56.52195	1	56.52195	1.17	0.2886
	ONS	52.07974	1	52.07974	1.08	0.3080
	ONAS	33.44303	1	33.44303	0.69	0.4124
4	Error	1352.62089	28	48.30789		
	PAN	2.94015	1	2.94015	0.18	0.6767
	PA	4.26787	1	4.26787	0.26	0.6157
	PS	6.30178	1	6.30178	0.38	0.5423
	PAS	11.58117	1	11.58117	0.70	0.4101
5	Error	463.71486	28	16.56124		
	OP	14.15556	1	14.15556	0.51	0.4808
	OPA	74.03935	1	74.03935	2.67	0.1135
	OPS	26.37406	1	26.37406	0.95	0.3378
	OPAS	32.03173	1	32.03173	1.16	0.2917
6	Error	776.44767	28	27.73027		
	NP	188.85608	1	188.85608	3.37	0.0771
	NPA	0.10223	1	0.10223	0.00	0.9662
	NPS	7.64979	1	7.64979	0.14	0.7146
	NPAS	4.28786	1	4.28786	0.08	0.7842
7	Error	1569.84729	28	56.06597		
	ONP	91.97702	1	91.97702	2.13	0.1557
	ONPA	12.10782	1	12.10782	0.28	0.6007
	ONPS	43.60023	1	43.60023	1.01	0.3237
	ONPAS	22.96790	1	22.96790	0.53	0.4720
8	Error	1209.79571	28	43.20699		

TABLE A-8. BMDP2V HEINOP 2N ANALYSIS OF MMEF**

ANALYSIS OF VARIANCE FOR 1st
DEPENDENT VARIABLE — MMEFP1 MMEFP2 MMEFP3 MMEFP4 MMEFP5 MMEFP6 MMEFP7 MMEFP8

	Source	Sum of Squares	Degrees of Freedom	Mean Square	F	Tail Probability
	Mean	27278.19339	1	27278.19339	60.22	0.0000
	Age	7351.41757	1	7351.41757	16.23	0.0004
	Sex	319.04958	1	319.04958	0.70	0.4085
	AS	688.44989	1	688.44989	1.52	0.2279
1	Error	12684.03371	28	453.00120		
	O3	18568.16773	1	18568.16773	43.08	0.0000
	OA	5222.09170	1	5222.09170	12.12	0.0017
	OS	809.82534	1	809.82534	1.88	0.1813
	OAS	265.69118	1	265.69118	0.62	0.4389
2	Error	12067.32311	28	430.97583		
	NO2	240.82473	1	240.82473	1.36	0.2526
	NA	470.07772	1	470.07772	2.66	0.1139
	NS	426.27319	1	426.27319	2.41	0.1314
	NAS	68.18274	1	68.18274	0.39	0.5393
3	Error	4942.54743	28	176.51955		
	ON	16.68042	1	16.68042	0.12	0.7363
	ONA	148.45950	1	148.45950	1.03	0.3189
	ONS	27.87588	1	27.87588	0.19	0.6635
	ONAS	42.02583	1	42.02583	0.29	0.5935
4	Error	4035.85561	28	144.13770		
	PAN	33.01697	1	33.01697	0.31	0.5808
	PA	180.71664	1	180.71664	1.71	0.2018
	PS	144.94590	1	144.94590	1.37	0.2516
	PAS	8.75579	1	8.75579	0.08	0.7757
5	Error	2961.23732	28	105.75848		
	OP	18.69390	1	18.69390	0.20	0.6600
	OPA	11.11805	1	11.11805	0.12	0.7343
	OPS	2.44565	1	2.44565	0.03	0.8734
	OPAS	304.48336	1	304.48336	3.22	0.0836
6	Error	2648.04157	28	94.57291		
	NP	283.77270	1	283.77270	1.19	0.2838
	NPA	7.28259	1	7.28259	0.03	0.8623
	NPS	29.85626	1	29.85626	0.13	0.7257
	NPAS	0.45976	1	0.45976	0.00	0.9652
7	Error	6654.69204	28	237.66757		
	ONP	44.01602	1	44.01602	0.32	0.5741
	ONPA	352.75621	1	352.75621	2.59	0.1186
	ONPS	30.44943	1	30.44943	0.22	0.6399
	ONPAS	75.65742	1	75.65742	0.56	0.4621
8	Error	3810.82287	28	136.10082		

APPENDIX B — SYMPTOMS REPORTED BY SUBJECT GROUP

Table B-1. NUMBER OF YOUNG MEN REPORTING SYMPTOMS

Symptom	FA	PAN	O_3	NO_2	PAN/O_3	PAN/NO_2	NO_2/O_3	PAN/NO_2/O_3
Unusual odor	0	1	1	3	3	2	5	6
Nausea	2	0	1	1	3	2	4	2
Cough	2	1	6	0	7	2	7	8
Sputum	2	5	4	1	4	3	5	5
Substernal soreness	0	2	4	0	3	0	3	2
Muscle soreness	0	0	0	0	1	0	1	1
Sore throat	2	1	4	1	5	3	6	2
Shortness of breath	0	0	3	1	6	1	3	5
Nasal discharge/ stuffiness	2	2	2	1	2	2	1	4
Wheezing	1	1	3	1	4	0	2	4
Tightness in chest	1	2	5	0	5	1	6	5
Dizziness	3	1	6	1	2	3	5	5
Fatigue	1	4	3	3	5	5	4	6
Eye irritation	0	2	2	0	3	4	1	1
Headache	2	2	0	0	4	3	4	2
Other	0	0	0	1	0	0	0	1
TOTAL	18	24	44	14	57	31	57	59

Table B-2. NUMBER OF YOUNG WOMEN REPORTING SYMPTOMS

Symptom	FA	PAN	O_3	NO_2	PAN/O_3	PAN/NO_2	NO_2/O_3	PAN/NO_2/O_3
Unusual odor	1	3	3	4	5	5	7	6
Nausea	0	0	0	0	1	1	1	2
Cough	2	1	5	3	8	2	7	4
Sputum	2	2	1	3	1	1	3	4
Substernal soreness	0	0	1	2	1	1	2	2
Muscle soreness	0	2	1	1	1	0	0	0
Sore throat	1	0	0	2	3	3	2	1
Shortness of breath	1	1	4	0	3	1	5	5
Nasal discharge/ stuffiness	1	2	0	3	2	1	3	1
Wheezing	1	0	0	0	2	0	0	2
Tightness in chest	2	2	7	2	6	4	8	6
Dizziness	0	4	3	1	4	3	3	2
Fatigue	4	2	2	5	3	3	5	6
Eye irritation	1	5	0	1	2	3	2	6
Headache	2	2	2	1	2	3	1	1
Other	0	0	0	0	0	0	2	0
TOTAL	18	26	29	28	44	31	51	48

TABLE B-3. NUMBER OF OLDER MEN REPORTING SYMPTOMS

Symptom	FA	PAN	O_3	NO_2	PAN/O_3	PAN/NO_2	NO_2/O_3	PAN/NO_2/O_3
Unusual odor	1	1	5	1	3	4	4	6
Nausea	0	1	1	1	2	1	1	2
Cough	1	2	3	2	4	2	5	7
Sputum	1	2	2	2	3	2	3	1
Substernal soreness	1	2	3	1	2	1	4	5
Muscle soreness	0	1	2	1	2	1	2	1
Sore throat	2	2	4	2	4	2	2	4
Shortness of breath	1	1	2	0	1	1	2	1
Nasal discharge/ stuffiness	1	2	2	2	3	4	2	1
Wheezing	0	1	1	0	1	1	2	3
Tightness in chest	1	1	3	1	3	1	3	4
Dizziness	1	1	1	1	3	1	2	2
Fatigue	2	4	4	3	5	2	3	6
Eye irritation	1	4	2	1	8	4	0	7
Headache	0	1	0	1	1	1	2	2
Other	1	3	3	0	2	1	2	3
TOTAL	14	29	38	19	47	29	39	55

TABLE B-4. NUMBER OF OLDER WOMEN REPORTING SYMPTOMS

Symptom	FA	PAN	O_3	NO_2	PAN/O_3	PAN/NO_2	NO_2/O_3	PAN/NO_2/O_3
Unusual odor	0	1	4	0	3	4	2	3
Nausea	0	0	0	1	1	0	1	0
Cough	3	2	4	1	5	2	5	5
Sputum	1	1	2	0	2	1	3	3
Substernal soreness	0	2	0	0	2	0	3	3
Muscle soreness	1	0	1	2	2	3	1	0
Sore throat	1	2	5	1	3	2	3	3
Shortness of breath	0	0	2	0	2	0	1	1
Nasal discharge/ stuffiness	2	3	3	1	2	1	2	3
Wheezing	0	1	0	0	0	0	1	0
Tightness in chest	0	0	3	0	3	1	1	2
Dizziness	0	1	3	1	4	1	1	2
Fatigue	2	4	5	3	4	3	4	5
Eye irritation	0	3	4	0	2	3	3	5
Headache	0	0	2	1	2	0	1	1
Other	0	0	2	1	2	2	0	3
TOTAL	10	20	40	12	39	23	32	39

HEALTH REVIEW COMMITTEE'S REPORT

HEI OBJECTIVES

JUSTIFICATION FOR THE STUDY BY HEI

Development of a close-knit community of well-trained scientists, whose research focuses on important environmental health issues relevant to automotive-generated air pollution, is one of the goals of HEI and its sponsors. Clearly, a study about the effects on humans of individual air pollutants, derived at least in part from automotive exhaust emissions, is relevant to HEI's mission. Although considerable data exists about the effects of ozone (O_3) and nitrogen dioxide (NO_2) on pulmonary functions in young men, as well as in some sensitive populations, little information exists as to the effects of these same pollutants on older men or women of any age. The Environmental Protection Agency set the current ambient ozone standard as 0.12 ppm for one hour, based on data primarily from young men(7)†. Obviously, it would be important to know whether or not there is sex- or age-related difference in sensitivity to an air pollutant as common as O_3.

OBJECTIVES OF THE PROPOSED STUDY

The report defines three primary objectives for the study: to investigate the possible interactions between O_3, NO_2, and peroxyacetyl nitrate (PAN) (i.e. does exposure to mixtures of O_3, NO_2, and PAN induce the same or different effects than those expected from the sum of the responses to exposure to each of these pollutants separately?); to compare the responses of men and women to oxidant pollutant exposure; to compare the responses of men and women between 18 and 30 years of age with those of men and women over 50 years of age.

In the study, eight men and eight women in two age groups, 18 to 26 years and 51 to 76 years, were exposed to filtered air and to seven pollutant regimes: O_3, 0.45 ppm; PAN, 0.13 ppm; NO_2, 0.60 ppm; O_3 + PAN, O_3 + NO_2; PAN + NO_2; O_3 + PAN + NO_2. Exposure lasted two hours and consisted of alternate 20-minute periods of rest and exercise. Forced vital capacity (FVC) and time-subdivisions of FVC were recorded five minutes after each exercise period. Minute ventilation ($\dot{V}_E$) was measured during the last two minutes of each exercise. Heart rate was monitored continuously.

RESULTS

1. Observable effects were associated with ozone exposures at 0.45 ppm. PAN and NO_2 caused no functional changes when administered individually, and did not augment the response to O_3. The investigators could demonstrate no effects of PAN (0.13 ppm) alone or in combination, whereas earlier, they reported a possible interaction with ozone at a PAN concentration of 0.13 ppm.
2. The results suggest little difference between the responses of men and women to O_3. Depending, however, on the method of analysis, one might suggest the possibility that women may be somewhat more responsive to O_3 than men.
3. The results also suggest that under the protocol used in this study, older people may be less responsive than younger people to O_3 exposure.

TECHNICAL EVALUATION

TECHNICAL REVIEW

The investigator clearly profited by challenges in the subject recruitment, the study design, and the data analysis presented by this study. Though well conceived and well carried out, this pilot study used small numbers of subjects, and therefore, did not allow for definitive conclusions. Similarly, since the population of subjects was not a random one, but rather was drawn from a solicitation for paid healthy volunteers, we cannot be sure whether or not one can generalize the results to all "normal" men and women of similar age. Finally, though the measurement of pulmonary function was handled well, a fully developed project in this area should include an expanded battery of tests.

The use of only one concentration of PAN (0.13 ppm) does not allow one to make any comment on the possible impact of a higher dose of PAN. The author's lack of a scale to measure the severity of subjective symptoms makes any analysis using symptoms assessment of limited value.

There is a great deal of uncertainty as to how to analyze and interpret the observations in women, regardless of their age. The current state of knowledge does not allow us to indicate the most appropriate method (if any) to normalize data so as to correct for the differences in lung volume and anatomy observed between men and women. Similarly, it is not clear that the author's comparison of the percentage change in pulmonary function from pre-exposure to post-exposure is the most appropriate measure upon which to rely.

The most interesting and potentially significant result concerns the diminished responsiveness of the older subjects. Although the observed differences herein might all be explained by the self-selection of participants, an effort to further explore this finding seems warranted, given the potential implications of such a conclusion to risk assessment and public policy.

† Refer to Notes on page 36.

CONCLUSIONS

This pilot study provided an excellent research experience for Dr. Drechsler-Parks. Although it did not settle any issue definitely, it does raise the question of possible sex- and age-related differences in responsiveness to air pollutants. Such issues deserve further clarification. Further study of the range of pulmonary function responses in "normal" individuals of varying ages seems warranted, as does research to determine the proper method or methods to equalize the effective doses of O_3 inhaled by different age and sex groups, and the proper method or methods to normalize pulmonary function (if any) so that appropriate comparisons can be made between men and women.

NOTES

1. 42 U.S.C. Section 7401-7642, 1982.
2. Section 202 of the Act, 42 U.S.C. Section 7521, 1982.
3. Section 112(a)(1) of the Act, 42 U.S.C. Section 7412(a)(1), 1982.
4. Section 211 of the Act, 42 U.S.C. Section 7545, 1982.
5. Section 303 of the Act, 42 U.S.C. Section 7603, 1982.
6. Section 109 of the Act, 42 U.S.C. Section 7409, 1982.
7. U.S. Environmental Protection Agency, 1986 Air Quality Criteria for *Ozone and Photochemical Oxidants*. Research Triangle Park, North Carolina: EPA Environmental Criteria for Assessment Office.

ABOUT THE AUTHOR

Deborah M. Drechsler-Parks received a doctorate in physical education, with a major in exercise physiology, from Pennsylvania State University in 1981. Her post-doctoral training, under the direction of Dr. Steven M. Horvath, was carried out at the Institute of Environmental Stress at the University of California, Santa Barbara, where she is presently an Assistant Research Physiologist. Dr. Drechsler-Park's research and publications emphasize the effects of air pollutant exposure on pulmonary function, and the effects of exercise and other environmental stresses on the respiratory system.

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