University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Adult Subjects

Medical IRB Study # 02-EPA-560
Consent Form Version Date: July 30, 2003

Title of Study: Physiological Changes in Healthy Young Adults Exposed to Concentrated Chapel Hill Coarse Air Particles

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Sponsor: United States Environmental Protection Agency

You are being asked to take part in a research study. The investigators listed above are in charge of the study; other professional persons may help them or act for them.

What are some general things you should know about research studies?

Research studies are designed to gain scientific knowledge that may help other people in the future. You may or may not receive any direct benefit from participating. There may also be risks associated with participating in research studies.

Your participation is voluntary. You may refuse to participate, or may withdraw your consent to participate in any study at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your doctor. If you are a patient with an illness, you do not have to participate in research in order to receive treatment.

Details about this particular study are discussed below. It is important that you understand this information so that you can decide in a free and informed manner whether you want to participate. You will be given a copy of this consent form. You are urged to ask the investigators named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

The purpose of this research study is to determine if people exposed to coarse particles normally present in the outdoor air develop temporary changes in their lungs or heart. To do this, we will expose volunteers to Chapel Hill air that we collect and concentrate on the day of the study. We will then analyze blood and lung samples and heart rhythms for evidence of inflammation, blood clotting abnormalities, and abnormal heart rhythms to help us determine what happens to people when they are exposed to air pollution. The levels of pollutants to which you will be exposed will not be higher than what you could be exposed to if you visited many major cities around the world. In a previous study conducted at our facility, we exposed young, healthy subjects, such as yourself, to fine particles. This exposure did result in some mild, temporary inflammation in the lung and some changes in the body's ability to form blood clots, but no changes in the heart tests. Because the particles you will be exposed to are larger, there is a chance that we will see similar inflammation in this study as well.

How many subjects will participate in this study?

If you decide to participate, you will be one of approximately fifteen 18-40 year old healthy adults in this study.

How long will your participation last?

Your participation in this study will last for approximately 5 weeks and you will need to visit our facility on 5 occasions. Each of these visits will last from 1 to 5 hours.

What will happen if you take part in the study?

During the course of this study, the following will occur:

You will be given a physical examination (lasting about 1 hour) to determine if you are eligible to participate in this study. This study requires that you have no significant problems with your nose, throat, heart, lungs, or blood. If you pass this physical examination we will schedule you for your first exposure session.

We will call you a few days before the exposure session to remind you of your scheduled visit. We will also remind you to refrain from alcohol, excessive amounts of caffeine, and from any activities where you could be exposed to high levels of pollutants (e.g. cigarette smoke, paint fumes) the day before your visit. Please report any pollutant exposure to the study personnel so you can be rescheduled if necessary.

The exposure day will last about 5 hours. You will report to the medical station in the Human Studies Facility where the nurses will take your temperature and ask questions about any symptoms or recent acute illnesses. You will be rescheduled if you have experienced an upper or lower respiratory tract illness within the past 4 weeks, or any other acute illness within the past week. Women will be asked about their latest menstruation and a urine pregnancy test will be conducted. If you are pregnant your participation will be terminated and you will receive full compensation for the exposure day. A small tube called a Hep-lock will be inserted into a vein in your arm remain in place until you leave for the day. This tube allows the nurses to easily draw blood from your arm before and after your exposure to air or particles. The nurses will also attach electrocardiograph (ECG) leads to your chest. It may be necessary to clean and shave the areas of you chest where these leads will be placed. The leads will be connected to 2 monitors (small recording devices about the size and weight of a portable tape player) to obtain readings of your heart rate and function. One of these monitors will be removed when you leave for the day. The other monitor, a Holter monitor, will remain connected to you until you return the next day. You will be asked to recline quietly for 30 minutes and to breathe at a constant rate while a measurement of your heart rate is taken by the Holter. It is important that you do not fall asleep during this 30-minute period. Next, a blood sample (about ¼ cup) will be taken from the Hep-lock in your arm and you will also be asked to blow into a tube to check the function of your lungs. In one of your visits, we will also determine the

amount of air that is moved into your lungs per minute (a test called minute ventilation) which will require you to ride a stationary bicycle and blow into a tube during the lung function measurements.

You will then enter the exposure chamber (4 x 4 x 6 feet in size) and be exposed to either clean air or air containing air pollution particles. The amount of particles you will be exposed to will depend on the amount of pollution in the air in Chapel Hill on the day of your exposure. While in the exposure chamber you will be asked to exercise on a bicycle ergometer 15 minutes, followed by 15 minutes of rest. This pattern will be repeated during the 2-hour period of time you are in the chamber. You will be directed to pedal at a speed fast enough to cause your heart to beat at about 120 BPM. A trained investigator will be seated outside the chamber to observe you at all times and a physician will be on call in the facility during the entire exposure session. During the exposure, your heart will be monitored. If it appears you are experiencing significant breathing or heart problems, or you develop any symptoms of discomfort (e.g. severe headache, nausea, vomiting, fever) the exposure will be stopped immediately. In addition, you may choose to stop the exposure at any time for any reason. If you do so, you will be paid in full for that day's session, but will be ineligible for further participation in the study and any payments you would have received for future participation. We may also elect to stop a study for any reason; however, if we do so, you will be paid in full for the entire study.

Immediately after the exposure you will again blow into a tube to determine if the exposure caused changes in your lung function. Then you will again recline quietly for 30 minutes while your heart rate is measured and another blood sample will be taken. The Hep-lock will then be removed and you will be allowed to leave. You will be asked to wear the Holter monitor with the electrodes attached to your chest until you return the next morning. It will take continuous readings from your heart during the entire time it is attached. You will not be able to shower or bathe until after the monitor is removed when you return the next morning. **In addition, it is very important that you take nothing by mouth (including water) after midnight. For your own safety, you will not be allowed to participate in the bronchoscopy if you do.**

The next morning you will return to the EPA facility for additional heart rate tests, blood-work, a pulmonary function test, and the bronchoscopy (about 5 hours). The nurses will check you in and a physician will ask if you encountered any difficulties overnight**.** A Hep-lock will be inserted into a vein in your arm and you will be allowed to rest quietly for 30 minutes for heart rate analysis, after which a blood draw will take place and the Holter monitor will be removed. Separate leads will be placed so that your heart rate and function can be monitored during the bronchoscopy procedure. You will then be asked to blow into a tube, like you did the previous day, to measure your lung function. The nurses will then lightly anesthetize your nasal passages and throat. A bronchoscope (similar a thin plastic tube) will be inserted through your nose and passed through the back of your throat to reach the trachea (windpipe) and the airways leading to the lungs. The bronchoscope has a tiny camera at its tip to assist the physician in the procedure. To reduce coughing and discomfort you will gargle and inhale an anesthetic (topical lidocaine) prior to beginning the procedure. During the procedure you will also receive supplemental oxygen. If any adverse reactions occur, prompt corrective action will be taken. After the bronchoscope is inserted, sterile saline will be used to wash out a small portion of your lung (about 1/64 of your lung). In addition a tiny brush with flexible bristles will be rubbed against the side of your airways a few times to remove some cells. Finally, if you opt to allow us to take a biopsy, a few small pieces of lung tissue (similar in size to a small grain of dry rice) will be removed from the wall of the airway leading to your lung using a tiny pair of forceps. These cells and tissues can only be obtained through the use of the bronchoscope and will be used to determine if air pollution particles affected the cells and fluids in your lung. You should not feel any pain during these procedures, though you may feel the urge to cough. Following the bronchoscopy, you will need to remain in the nurses' station for a suitable observation period. During this observation period you will be offered snacks and drinks once it is safe for you to eat and drink. When a physician has determined that you are fully recovered you will be discharged.

Are there any reasons you should not participate?

You should not participate in this study if you are unhealthy or pregnant. You need to be non-smoker for at least 1 year prior to the study and have not smoked or smoked only a little earlier in your life. There are several medical conditions that may prevent you from participating in this study. These include, but are not limited to, active allergies or other pulmonary diseases, diabetes, need for a pacemaker, a previous heart attack or coronary bypass surgery, dialysis treatment, or the need for supplemental oxygen. In addition, if you take certain medications, (either prescription or over-the-counter) that may affect our ability to interpret your response to particles you will be asked to stop taking them for 2 days prior to your exposure sessions. These may include things such as anti-inflammatory drugs such as aspirin or anti-oxidants. If you are unable to stop taking your medications, you will not be eligible for the study

What are the possible risks or discomforts?

This study might involve the following risks and/or discomforts to you:

If you have any tendency to become uncomfortable in small closed spaces, it is possible that you may become uncomfortable during this study. You will be taken to the exposure chamber when you are first evaluated for suitability for the study to allow you an opportunity to see where you will sit and what the chamber looks like.

During one of your exposure sessions you will be exposed to air pollution particles. Some studies suggest that elderly people, particularly those with underlying cardiovascular disease, may be at increased risk for developing illness or even dying as a result of exposure to particles. However, the risk is much less for young healthy people. At this time, no one understands exactly how particles might cause increased risk of disease or death, but the risk to any one person, especially a young healthy person, are extremely small. While we cannot exclude the possibility that you may have an adverse reaction to breathing these particles, you will only be exposed to them for a 2-hour period and they will not exceed levels you might encounter if you were to visit many major cities around the world on a smoggy day.

There are minimal risks associated with the lung function measurements in which you blow through a tube. One of the lung function tests requires that you inhale a gas mixture containing 0.3% carbon monoxide, 0.3% methane, and 0.3% acetylene. Inhalation of high concentrations of carbon monoxide over several minutes may cause headache, nausea, and dizziness. Methane is an inert gas and has small effects at high concentrations. Acetylene is a gas that at high concentrations may cause headache and dizziness. However, the concentrations of the gas mixture you will inhale are quite low and you will inhale them only for a very short time. The inhalation will be stopped immediately should you develop any of the following symptoms: headache, nausea, dizziness or general discomfort.

There are minimal risks associated with monitoring your heart by ECG or blood oxygen by pulse oximetry. Preparing your skin for placement of ECG electrodes and removing the electrodes the next day may cause some irritation, itching, or burning in some people. If this occurs you should call the nursing staff.

The risks associated with taking blood samples are considered minimal. A qualified member of the staff will place an IV catheter (Hep-Lock) in your arm, which could cause some minor pain, which usually resolves very soon after the catheter is in place. Placement of an IV catheter can result in the formation of a bruise at the site of the IV after it is removed. Also, a rare complication of IV placement is skin infection or an infection of the vein in which the IV catheter has been placed. The risk of getting an infection from the IV is minimized by the use of sterile technique to place the catheter. If you do have signs of infection at the IV site (redness, warmth, painful skin, swelling) after completion of the

procedure, you will need to contact the EPA medical station or the physician who performed the bronchoscopy.

There are several risks associated with performing bronchoscopy. The primary risk of bronchoscopy is coughing and discomfort in the nose and throat, which is caused by having the bronchoscope inserted through the nose and passed through your throat. This discomfort and coughing is alleviated with topical lidocaine, which you will gargle and inhale prior to beginning the procedure. If you are unable to tolerate the passage of the bronchoscope through your nose and throat because of pain or uncontrollable coughing in spite of having received the maximum allowable amount of lidocaine, the procedure will be immediately terminated.

The lidocaine used for anesthesia during the procedure may result in some adverse effects due to absorption into the blood stream from the nose and the lungs. Lidocaine can cause symptoms in your central nervous system (confusion, tremor, euphoria, or, rarely, seizure) or heart rate disturbances (very fast or very slow heart rate) if an excessive dose of medication is used. The topical doses of lidocaine in this study will be low (300 milligrams) so we do not expect significant systemic absorption to occur. If you are allergic to lidocaine, you could develop itching, hives, difficulty breathing, and possibly shock (a drop in blood pressure). This risk is minimal, but you will be excluded from the study if you are allergic to lidocaine or any other topical anesthetic that is commonly used in minor surgical or dental procedures. You should know that a volunteer receiving a large lidocaine overdose (over 1000 milligrams) during bronchoscopy in Rochester, New York died as a result of the overdose. However, no serious side effects of this medication have been noted at lower doses such as those described in this protocol and one of the nurses who assist during the bronchoscopy carefully monitors the amount of lidocaine to which you are exposed. If an adequate level of anesthesia is not reached with 300 milligrams, the procedure will be stopped.

On very rare occasions, bronchoscopy can cause an asthmatic attack, characterized by wheezing, chest tightness, and shortness of breath. This type of complication is very, very rare in subjects who have no history of asthma or other lung diseases. If an asthma attack occurs, the bronchoscope will be removed, and inhaled medication used to treat asthma (e.g. albuterol) will be given. These steps are usually all that is necessary to terminate the attack. However, if further care is needed, you will be transferred by ambulance to the Emergency Room at University of North Carolina Hospital.

Bleeding from the nose can also occur as a result from bronchoscopy. It is usually caused by injury from the bronchoscope within the nostril. This type of bleeding is almost always very minor, causing streaking of the nasal mucus, which resolves spontaneously within an hour or so after completion of the bronchoscopy. On extremely rare occasions, moderate to severe nose bleeding would require packing your nose with sterile gauze and transferring you to the Emergency Room at University of North Carolina Hospital. Aspirin products (including BC Powders or Goodys Powders) and anti-inflammatory medications such as Motrin (ibuprofen) and Naprosyn (naproxen) may cause an increased tendency to bleeding. It is essential that you not take these types of medications for at least one week prior to bronchoscopy (acetaminophen [Tylenol] is acceptable).

Another risk that can occur from performing bronchoscopy is pneumothorax (collapsed lung). This may occur when biopsies (tissue samples) are being taken. In the very unlikely event that a pneumothorax does occur, you must be aware of the symptoms that it can cause: chest pain and shortness of breath. If these symptoms do occur after your bronchoscopy, you must contact the EPA physician who performed the bronchoscopy immediately. His name and telephone number are on the discharge sheet you will be given when you leave the facility. If pneumothorax occurs after bronchoscopy, it usually occurs within 24 to 48 hours after the procedure is completed.

Some subjects who undergo bronchoscopy may have a low-grade fever (less than 101 degrees Fahrenheit) after the procedure is completed. This fever is almost always benign, and it occurs in approximately 25 percent of all subjects who undergo bronchoscopy. This fever usually resolves within 24 hours with the use of Tylenol. Nevertheless, a persistent fever or any temperature of greater than 101 degrees Fahrenheit might mean that you have an infection. Therefore, if you have any fever greater than 101 degrees Fahrenheit after the bronchoscopy or a fever that doesn't resolve within 24 hours after the procedure is completed, you should contact the physician who performed the bronchoscopy so that arrangements can be made for you to be examined.

Finally, there is a small possibility (less than 1 percent) that you might get pneumonia as a result of bronchoscopy in which bronchoalveolar lavage is performed. The signs and symptoms of pneumonia include: 1) fever greater than 101 degrees Fahrenheit or persistent fever, 2) persistent cough with or without sputum production, 3) chest pain, 4) shortness of breath with exercise or at rest, 5) coughing up of blood. If you experience any of these symptoms after bronchoscopy, you should contact the EPA medical station or the physician who performed the bronchoscopy so that arrangements can be made for an examination by an EPA physician. You will be contacted 24 to 48 hours after the bronchoscopy to see if you are experiencing any of the above mentioned problems or any new health problems that you think could be related to bronchoscopy.

In addition, there may be uncommon or previously unrecognized risks that might occur.

What are the possible benefits?

There are no direct benefits to you for participation in the study, although you will receive a medical examination that includes blood work, lung function testing, and baseline ECG at no charge. However, this is not a substitute for a routine doctor visit. A member of the medical staff will explain to you any remarkable findings regarding your overall health status. In addition, if we observe changes in your heart rate or lungs as a consequence of exposure to air pollutants, you may elect to use this information to avoid exposure on high pollution days. The primary benefit to society produced by this study will be a better understanding of whether or how air pollution particles affect people. Given that every member of American society is currently exposed to these pollutants, this study has the potential to contribute to devising effective strategies aimed at protecting millions from the untoward effects of these particles.

What if we learn about new risks during the study?

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

How will your privacy be protected?

No subjects will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-CH will take all steps allowable by law to protect the privacy of personal information.

Will you be paid for participating?

You will be paid $15.00 for time spent in your initial interview to determine if you are interested and qualify to participate in the study. In addition you will be paid $15.00 for your physical examination. If you qualify for the remainder of the study, you will receive payment for your participation at the rate of $12.00 per hour. You will need to be at the Human Studies Facility approximately 5 hours for each exposure session, including 2 hours in the exposure chamber itself. You will also need to return to the EPA facility the next morning for follow-up procedures which will take about 5 hours. You will also be paid $25 every time we draw blood during the study and $100 every time you wear the Holter monitor overnight. You will be paid up to $400 for each bronchoscopy, which will include washing a small

portion of your lung with sterile saline, obtaining a small number of cells with a cytology brush, and removing a small biopsy sample ($350 if you decide against the biopsy). You are also entitled to a $50 bonus if you complete the entire study. The total compensation if you complete this study should be approximately $1382. In addition, you will be reimbursed for reasonable travel expenses and for parking costs at the UNC campus.

The following table details the expected compensation for completion of the entire study:

Initial Screening for Eligibility		$15
Physical Exam		$15
Bronchoscopy Physical Exam		$20
Training		$12
Exposure Sessions (2 for 5 hours each)		$120
(Check-in, pre-testing, exposure, post-testing)		
Blood samples (6)		$150
24-hour holter monitor (2)		$200
Bronchoscopy (2)		$800
BAL	$650	
Brushes	$50	
Biopsis	$100	
Bonus for Completing the Study		$50
Total Compensation		**$1382**

It is possible that on some days (e.g. when it is raining) there may not be enough air pollution particles in the air to allow the study to proceed. If that happens during one of your visits, you will be rescheduled and receive double compensation ($24/hr) for the time you had to spend at the EPA facility that day. In addition, you will be reimbursed for reasonable travel expenses and for parking costs at the UNC campus.

You understand that your participation is voluntary. You may terminate your participation in the study at any time without penalty, and without losing benefits you would otherwise be entitled to. If you elect to terminate your participation in the study or if we are unable to perform a procedure or complete the study due to your noncompliance with our instructions, you will be paid for that portion of the study which has been completed. The investigators also have the right to stop your participation in the study at any time. This could be because you have had an unexpected reaction, or because the entire study has been stopped or for some other reason. If this occurs, you will be paid for the entire study.

Will it cost you anything to participate?

The U.S. EPA will pay the costs of this research. You will not be billed for any procedures.

What will happen if you are injured by this research?

All types of research involve possible risk, some including the risk of personal injury. In spite of all precautions, you might develop complications from participating in this study. If such complications arise, the researchers will assist you in obtaining appropriate medical treatment, but any costs associated with the treatment will be billed to you and/or your insurance company. The University of North Carolina has not set aside funds to compensate you for any such complications or injuries, or for related medical care. However, by signing this form you do not waive any of your legal rights.

In the event of personal injury resulting directly from the research procedures, financial compensation cannot be provided under the Federal Employee Compensation Act. In the event that physical injury is caused by the negligence of a federal employee, the federal government would be liable in accordance with the Federal Tort Claims Act (28 U.S.C. 2671-2680).

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have further questions, or if a research-related injury occurs, you should call one of the listed investigators:

Don Graff, Pharm.D.	919-843-5155
Robert Devlin, Ph.D.	919-966-6255
Tony Huang, M.D.	919-843-9504

What if you have questions about your rights as a subject?

This research has been reviewed and approved by the Committee on the Protection of the Rights of Human Subjects (Medical IRB) at the University of North Carolina at Chapel Hill. If you have any questions or concerns regarding your rights as a research subject, you may contact the Chairman of the Committee at (919) 966-1344.

Medical IRB Study # 02-EPA-560

Title of Study: Physiological Changes in Healthy Young Adults Exposed to Concentrated Chapel Hill Coarse Air Particles

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Subject's Agreement:

I have read the information provided above. I voluntarily agree to participate in this study.

____ ___________________
Signature of Research Subject Date

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Printed Name of Research Subject

____ ___________________
Signature of Person Obtaining Consent Date

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Printed Name of Person Obtaining Consent