THIS CONSENT DOCUMENT SHOULD BE USED ONLY
BETWEEN 7-23-10 AND 9-27-10
INSTITUTIONAL REVIEW BOARD, UNC-CHAPEL HILL

University of North Carolina-Chapel Hill

Consent to Participate in a Research Study and Consent for Genotype Screening
With Identifying Information
Subjects 18 years of age or older
Biomedical Form

IRB Study:# 09-1625
Consent Form Version Date: July 21, 2010

Title of Study: Epigenetic effects of diesel exhaust and ozone exposure

Principal Investigator: Melanie J. Jardim, Ph.D., David Diaz-Sanchez, Ph.D. and Kelly Duncan, Ph.D.
Department: United States Environmental Protection Agency
Phone number: 919-966-7320

Co-Investigators: Michael T. Schmitt, MSPH

Sponsor: U.S. 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 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 ability to participate with EPA-sponsored research.

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 understand how ozone exposure compares to that of diesel exhaust exposure in order to investigate mechanisms of injury by environmental pollutants. This may be especially important for asthmatics, because studies have shown an association between exposure to air pollution and increased medication usage and emergency room visits in this population. To accomplish this we will:

- Document changes in lung function (spirometry) and the presence of mild inflammation in the respiratory tract (measured by bronchoscopy to collect cells from the lower respiratory tract) after each exposure.
- Determine if air pollution exposure can affect components of the blood involved in inflammation and clotting.
- See if air pollution particles can cause changes in the ability of the nervous system to correctly regulate one's heart rate.
- Cells from your airways will be collected and stored. All specimen collections will be stored throughout the course of this study and then any remaining samples will be stored indefinitely as described in an accompanying consent form ***Consent for Storing Biological Specimens <u>With</u> Identifying Information.***
- The cell samples will be used to identify the expression of a panel of inflammation- and oxidative stress-related genes. As new genes are identified that may be associated with adverse health effects of air pollutant exposure, expression of these genes may also be investigated.
- The cell samples will be used to identify epigenetic changes (mechanisms which control the expression of genes) associated with air pollutant exposure.
- Research reports have suggested that people with particular genes are more susceptible to air pollutants. The cells will be studied for those specific genes related to adverse health effects of air pollutant exposure.

<u>Are there any reasons you should not participate?</u>

You should not participate in this study if:

- You are pregnant, attempting to become pregnant or nursing an infant
- You have a history of significant chronic illness other than asthma, or your asthma is not well-controlled
- You are not 18 to 55 years of age
- You cannot perform intervals of moderate exercise
- You are not fluent with the English language
- You are taking more than 81 mg aspirin regularly
- You are unwilling or unable to refrain from the following medications for the week prior to the study: anti-inflammatory agents such as ibuprofen (Advil), naproxen (Aleve, Naprosyn) or aspirin
- You have skin allergy to tape or electrodes
- You are currently taking or have taken anti-coagulant medication in the week prior to the study
- You are currently smoking or have a smoking history within 2 years of the study
- You have been diagnosed as a severe asthmatic as defined by physician-directed emergency treatment for an asthma exacerbation within the preceding 12 months, use of systemic steroid therapy within the preceding 12 months, nighttime symptoms of cough or wheeze greater than 2 times per month, asthma symptoms (cough, wheeze, chest tightness) more than 2 times per week, requirement for albuterol due to asthma

symptoms more than 2 times per week, (not including prophylactic use of albuterol prior to exercise), have chronic and continuous allergic rhinitis.

- Your dosing level of an inhaled steroid is not consistent with the severity of your asthma as outlined by the NHLBI NAEPP guidelines
- You have a history of fainting in response to pain
- You currently have or have had a viral respiratory tract infection or any acute infection requiring antibiotics within 6 weeks of the study. If this is the case, your visit will be rescheduled
- You currently have or have had seasonal exacerbation of allergic rhinitis symptoms within 1 weeks of the study. If this is the case, your visit will be rescheduled

You should not participate if you are unable to comply with the following requirements:

- No over the counter pain medications such as aspirin (aspirin $\leq$ 81 mg/day is allowed), Advil, Aleve or other non-steroidal anti-inflammatory medications for 7 days prior to all visits. Tylenol (acetaminophen) is permitted.
- No vitamin C or E (or multivitamins which contain Vitamins C or E) for 7 days prior to all visits.
- Avoid smoke and fumes for 24 hours before all visits.
- Avoid drinking alcohol 24 hours before all visits.
- Avoid strenuous exercise for 24 hours prior to and after all visits.
- Avoid eating or drinking anything after midnight on the evening of the Exposure Day 1, before the bronchoscopy to take place on Exposure Day 2.
- No caffeine for 12 hours prior to all study visits.
- Avoid use of antihistamines for one week prior to exposures.

How many subjects will participate in this study?

If you decide to participate, you will be one of approximately 60 subjects in this research study.

How long will your participation last?

Your participation in this study may require up to 9 visits to the research facility over approximately 6 months if you are eligible for the study.

What will happen if you take part in the study?

Before you agree to participate in this study, you must read the consent form in its entirety. The research and medical staff will then answer all of your questions and explain all of the risks involved in this study to your satisfaction.

You should have already undergone a general screening visit and physical examination, and a physical exam and pulmonary function test for bronchoscopy to certify that you are a suitable candidate. For the exposure study, we will perform the following procedures:

Training Day

- Report to the EPA medical station at the requested time.
- We will review the inclusion and exclusion criteria and any medical conditions that you have or medications that you are currently taking. We will go over the study in detail so that you will know what we will expect from you as a participant and what you should expect from us as investigators. If you agree to participate in the study you will sign 2 copies of this consent form. We will give one copy to you. We will check your vital signs (heart rate, respiratory rate, blood pressure, oxygen saturation level and a symptom questionnaire) and do a pregnancy test if applicable(WOMEN ONLY) For the pregnancy test, you will be asked to provide a urine sample. The purpose of this test is to provide evidence that you are not pregnant at the time of the study. The nurse will also ask you when your most recent menstrual cycle began. The results of the pregnancy test will be held in strict confidence. A positive pregnancy test will preclude further participation.
- You will undergo a breathing test. This is known as spirometry, and you will breathe through a filter into the machine. We will coach you, and you will be asked to take a full breath in and then blow it out as hard and fast as you can. We will ask you to do this several times. The information gained from the breathing tests will be used by the investigators to determine whether you qualify for the study.
- You will be trained on the exercise bike and the work load to elicit a minute ventilation normalized for body surface of $25L/m^2/BSA$ will be determined.

Exposure Day 1: You will be asked to eat a normal breakfast and arrive at the EPA medical station no sooner than 8 am. You will need to wear comfortable clothes and shoes, and bring a lunch.

Prior to exposure, you will:

- Have your vital signs checked (heart rate, respiratory rate, blood pressure, oxygen saturation level) and fill out a symptom questionnaire. Have a pregnancy test if applicable.
- Have monitors placed on you so that we can watch your heart rate and rhythm. One of these monitors will be removed at the end of the day and the other monitor will be kept on for 24 hours. Before exposure, after exposure and the following morning during your next visit to the facility, there will be a 30 minute measurement of your heart rate. This will consist of a 20 minute rest period and a 10 minute data collection. The monitor will be removed after the last data collection. These monitors will allow us to determine if air pollutants cause small changes in the ability of your nervous system to regulate how your heart beats.
- Have up to 80 mL blood drawn (about 5 tablespoons). We will test this blood to see if diesel exhaust or ozone exposure affects the ability of your blood to clot correctly, and to look at changes in proteins and/or blood cells.
- Have a breathing test (spirometry). You will breathe through a filter into the machine. We will coach you, and you will be asked to take a full breath in and then blow it out as hard and fast as you can. We will ask you to do this several times.
- Given a Symptom Questionnaire for you to fill out.

- Testing will be postponed if it is determined that your medication history is not within previously established limits, respiratory tract illness has occurred within the previous 6 weeks or if respiratory symptoms are present.

During the exposure, you will:

Undergo a chamber exposure of 2 hours duration, once to clean air, once to diesel exhaust and once to ozone; the amount of pollution you will be exposed to is less than what you would likely encounter over 24 hours on a smoggy day in an urban area. You will be blinded as to the exposure condition. The exposure chamber is 6 ft wide by 6. ft in height, and is 8 ft in length. Chamber conditions will be at a comfortable temperature and relative humidity. A physician or other trained person will be seated outside the chamber observing you at all times. During the exposure, your heart will be monitored and the amount of oxygen present in your blood will be monitored by placing a device (pulse oximeter) on your finger. You will exercise for 15 minutes at the previously determined pace and rest for 15 minutes. While exercising, minute ventilation may be measured intermittently. Your blood pressure may also be measured intermittently. If it appears you are experiencing significant discomfort, breathing or heart problems, the exposure will be terminated immediately. **In addition, you may elect to terminate the exposure at any time for any reason.** If you do so, you will be paid for your participation up to that point, but will be ineligible for further participation in the study and any payments you would have received for future participation.

Following the exposure, you will:

- Have a breathing test (spirometry). You will breathe through a filter into the machine. We will coach you, and you will be asked to take a full breath in and then blow it out as hard and fast as you can. We will ask you to do this several times.
- Have your vital signs checked.
- Have a reading of your heart rhythm taken with the Holter monitor.
- Fill out a symptom score sheet.
- Have blood drawn (up to 80 mL or about 5 tablespoons).
- Be assessed and discharged by the nursing staff.

Exposure Day 2 (24 hour follow up visit): You will come back the next morning and asked to arrive at the EPA medical station at no sooner than 8 am. (approximately 24 hours after exposure) You will:

- Have your vital signs taken.
- Fill out a symptom questionnaire.
- Have blood draw (up to 80 mL or about 5 tablespoons).
- Have spirometry testing.
- Have a reading of your heart rhythm taken with the Holter monitor.
- Have the Holter monitor removed.
- We are asking all subjects to have bronchoscopy on the day following each exposure. If you are an asthmatic, prior to the bronchoscopy you may be pretreated with inhaled bronchodilator (albuterol). The bronchoscopy will not be performed if the baseline lung function shows more than a minimal amount of airway obstruction and this does

not resolve with inhaled bronchodilator. During the bronchoscopy, a fiberoptic scope will be inserted through the nose into one of your airways where a portion of one of your lungs will be washed with sterile saline and a sample of airway lining cells will be obtained with a special brush device.

Bronchoalveolar Lavage (BAL) and Brush Biopsy is frequently used in the diagnosis of lung disease in both adult and pediatric patients. The procedure has also been used in numerous research studies of persons with respiratory disease and in healthy volunteers. The procedure has been used safely many times in studies conducted at our laboratory. The purpose of the BAL procedure is to obtain fluids and cells from the lower regions of the respiratory tract, i.e., the trachea, bronchi and smaller airways. These materials will be analyzed to obtain information about the role of various chemical substances and cells in the pulmonary response to particle exposure of persons with asthma. The bronchoscope is a flexible fiberoptic tube that is about two feel long and 1 centimeter in diameter (about the diameter of a pencil). It is an optical device with a light at the end which can be used to transmit images to a camera connected at the other end. Using the bronchoscope, the physician can see into your airways and direct the placement of the bronchoscope. A small channel allows fluid to pass through the bronchoscope.

The BAL procedure will be performed at the laboratory medical station by specially trained experienced pulmonary physicians. You will be expected at the medical station at 8:00 on the morning after the exposure. If you have had anything to drink or eat since midnight the night before the bronchoscopy you will not be allowed to proceed. Before you undergo bronchoscopy, your lung function will be evaluated and if you are an asthmatic you may be treated with inhaled bronchodilator (albuterol). The procedure will not be performed if your lung function does not meet a predetermined level of function recommended by the National Institute of Health for performing research bronchoscopies in persons with asthma. You may terminate the bronchoscopy procedure at any time. If the physician determines an increase level of anxiety, the procedure will be terminated

A saline lock intravenous catheter will be placed in a vein in your arm to give you medication before the procedure starts (a saline lock is a flexible catheter that stays in your arm for a short time). The saline lock will remain in place so that it can be used to administer medications in case medications need to e administered during the procedure. You will also be connected to a telemetry monitor that will display heart rate and rhythm, a blood pressure cuff will be placed on your arm, and an oximeter sensor (small band like device will be placed on a finger to allow the medical staff to monitor your oxygen levels during the procedure. No sedatives and/or narcotics will be administered at any time during bronchoscopy.

Before proceeding, the medical staff will again make certain that you have had nothing to eat or drink since midnight the previous night. You will be asked to decongest your nose by administering 2 puffs of neosynephrine nasal spray to each nostril. They will then give you a lidocaine solution and ask you to gargle with it for about two minutes to anesthetize your throat. You will then be asked to inhale (snort) a small amount of lidocaine jelly through both nostril to anesthetize your nose and the back of your throat. A Q-tip with lidocaine jelly will be gently inserted into your nose

to ensure that your nose is completely numb before the bronchoscope is inserted. The procedure will not begin until your nose and throat are well anesthetized. If this cannot be accomplished, the bronchoscopy will not be performed. A tube delivering oxygen will be placed inside your other nostril. Delivery of supplemental oxygen is done as a precaution during all bronchoscopies conducted at our facility.

To start the procedure, the physician will pass the bronchoscope through your anesthetized nostril to the back of your throat and then to above your vocal cords. The pulmonologist will then inject a lidocaine solution to numb your vocal cords before passing the bronchoscope into your trachea (windpipe). More lidocaine, up to a safe maximum dose is injected at various points in your trachea and airways to minimize coughing during the procedure. You will experience some cough during the procedure. This is a normal reflex caused by the presence of the bronchoscope in your airway.

Brush biopsies of your airway epithelium will be taken from the major lower airway passages. A very small brush (3 millimeters in diameter) will be inserted through the channel in the bronchoscope. The brush is visible to the physician performing the procedure through the bronchoscope. Small amounts of surface cells are scraped from the airway by gently brushing the the wall of the airway several times. Up to 8 brush biopsies are taken.

BAL will be performed by gently wedging the bronchoscope in a small airway of the right lung. Sterile saline will be injected in your lung through a channel in the bronchoscope. The saline will then be gently suctioned from your lung through the channel in the bronchoscope. This sequence will constitute a wash. A total of up to 250 cc (about 20 tablespoons) of sterile saline will be used during the BAL procedure. Approximately 75% of the saline injected into your lungs will be recovered by aspiration (suction) through the bronchoscope. The remaining 25% is expected to remain in your lungs. The saline left in your lungs will not generally cause you any difficulty breathing or harm you and should be completely absorbed by your lungs within 48 hours.After the wash and brush biopsies are obtained, the procedure will be complete and the bronchoscope will be removed from your airway. The total time the bronchoscope will reside in your airways will be up to 30 minutes.

After the procedure the oxygen catheter will be removed if your oxygen saturation is acceptable. The nurses will check your vital sign immediately after the procedure and every half hour thereafter until discharge. During this time you will sit in a recliner at the medical station for an observation period of approximately two hours. You will not have any food or drink during this time. After the recovery period, the nurses will check your gag reflex. Since the gag reflex will be absent due to anesthesia during the procedure, you will not be allowed to ear or drink until the anesthesia wears off. This normally takes about one to one-and-one half hours. Once your gag reflex returns, you will then be given some juice to sip and then some food.

The physician who performed the procedure will check you after the recovery period and you will repeat the spirometry lung function test. You will be discharged if your vital signs are stable, chest examination is normal If you are an asthmatic, before you are discharged, you may perform spirometry and your lung function should be equal to or greater than 80% of your pre-procedure value. Prior to discharge you will be requested to take 600 mgm of ibuprofen by mouth; administration of

ibuprofen/motrin almost always prevents the post-bronchoscopy malaise and low grade fever that would otherwise occur in about 25% of persons undergoing the procedure (acetaminophen/tylenol is a less effective alternative medication).

Before going home, you will be give the phone number of the medical station (966-6232) and pager phone numbers for the physician who performed the bronchoscopy with instructions to call if you experience any adverse symptoms such as: 1) persistent fever or fever above 101 degrees Fahrenheit, 2) persistent cough, 3) sputum (phlegm) production, 4) chest pain, 5) coughing up any amount of blood, 6) nose bleeds, or 7) shortness of breath

Are there any reasons you should not participate in bronchoscopy?

You should not participate in this study if you have problems with excessive bleeding after minor cuts or abrasions. You should not participate if you have had a recent exacerbation in your asthma that was not controlled with your usual medications. The physician and medical staff will explain other exclusionary condition in detail to you. In addition, during your participation in this study, you will be asked to refrain from, limit, or control taking the following medications:

*No more than 81 mg aspirin or similar medication on a regular basis or during the week of testing.
*Withhold antihistamines for 7 days prior to testing.
*Withhold inhaled bronchodilators 12 hours prior to testing.
You should not participate in this study if you are unwilling or unable to remain in the local area for 24 hours following each bronchosocpy

With your permission, DNA from the collected cells will be genotyped for specific genes related to adverse health effects associated with air pollution exposure. Unwillingness to have samples genotyped will NOT exclude you from participating in the study. If you do not wish for your cells to be used for genotyping but do wish to participate in the study do not sign the section ***Subject's Agreement for Genotype Screening With Identifying Information*** located at the end of this document.

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.

If there are any samples left over after all study information is collected, we will continue to store the samples for as yet undesignated studies. You will be given a separate consent form for this storage, and you do not have to allow your samples to be stored indefinitely. With your permission, we will continue to store any samples that we collect to possibly use for other studies. This allows us to make the best use of the samples we collect from our volunteers. Again, you do not have to allow us to keep these samples if you do not want to.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. You will not benefit

personally from being in this research study. We will share with you any information that we learn about your lung function or other medical findings. We can also send you the results of some of the blood tests we perform.

What are the possible risks or discomforts involved with being in this study?
This study might involve the following risks and/or discomforts to you:

1. Blood sampling will be performed by well-trained personnel, and entails only a risk of mild discomfort with the infrequent possibility of lightheadedness, fainting, infection or developing a bruise.

2. Breathing tests (spirometry): You may cough or become dizzy during these tests. You will be seated in a chair, and if these symptoms occur, they are usually only temporary. Also, the forceful breathing during this test can cause wheezing or shortness of breath to occur.

3. The adhesive patches used as part of the heart monitoring system may cause some mild skin discomfort or discoloration. If this occurs you should notify the nursing staff.

4. During air pollution exposure, you may experience some minor degree of airway irritation, cough, shortness of breath or wheezing. Some studies suggest that persons with asthma may be at risk for developing an asthma attack as a result of exposure to fine air pollution particles. These symptoms typically disappear 2 to 4 hours after exposure, but may last longer for particularly sensitive people. Your symptoms will be closely monitored during the exposure and the study terminated if more than modest respiratory symptoms occur during the exposure. In the unlikely event that you develop medically significant symptoms, the exposure will be terminated and the appropriate medical intervention will be provided if required. A physician is always available to respond to an emergency and full resuscitation equipment is available for use in the event of a cardiac or pulmonary emergency. If you experience a significant drop in your lung function, albuterol will be administered.

Air pollution may induce an inflammatory reaction that can last for 24 hours after exposure and may increase the chance of you catching a cold. You should not engage in heavy levels of exercise for 24 hours before and after the exposure period. There is a small possibility that you could have more asthma symptoms for several days, and even less likely, for several weeks, after the particle exposure. This flare in your asthma would be similar to what happens to you and other asthmatics during the allergy season or with a viral infection. Such a flare is considered highly unlikely and the exposure risk is comparable to walking around a major metropolitan area such as Los Angeles or Houston on a smoggy day. If an asthma flare occurs, you will be asked to seek medical treatment from your regular physician who treats you for your asthma.

If you have any tendency to become uncomfortable in small closed spaces, it is possible that you may become uncomfortable during the chamber exposure. 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. The chamber dimensions are 6 ft in width, 6 ft in height, and 8 ft in length. Although the chamber is somewhat small, it has multiple windows and you will be in constant visual contact with the investigator who will be monitoring you during the exposure. You also will be able to verbally communicate with the investigator at all times.

5. Bronchoscopy: As with other medical procedures, there are risks associated with bronchoscopy. However, experience has shown these risks are extremely small in research subjects. The risks associated with bronchoscopy are described in detail below.

A primary risk is bronchoscopic procedures is **discomfort to the nose and throat** brought about by the insertion of the bronchoscope through the nasopharynx. This discomfort should be alleviated or eliminated by the use of local anesthetics such as lidocaine. For this reason, you will be asked to gargle with a lidocaine solution and have lidocaine jelly placed in your nose prior to beginning the procedure. The effectiveness of the anesthesia will be tested by using a cotton swab gently inserted into your nose before inserting the bronchoscope. If you experience pain or discomfort during insertion of the bronchoscope, more lidocaine will be used up to a safe maximum amount. If adequate anesthesia cannot be achieved using this amount of lidocaine, the procedure will not take place.

A second risk of bronchoscopy is **coughing** that results from the irritation of the airway caused by the presence of the bronchoscope in the airway. Coughing is a normal reflex to expel foreign substances from the airways. Because coughing itself can cause mild trauma and discomfort to the airways and vocal cords, lidocaine liquid is sprayed on the airways at various sites to suppress the cough reflex. This technique is usually not completely successful and it is expected that you will have some cough during the procedure, especially during the initial insertion of the bronchoscope into the airway. If coughing is not controllable with the lidocaine or causes you discomfort, the procedure will be terminated.

There is a slight chance that the bronchoscopic procedure will precipitate an **asthma attack**. This risk is minimized by 1) only allowing persons with mild stable asthma to participate in the study, 2) pretreatment with inhaled bronchodilator (albuterol) before the procedure if your lung function is impaired and 3) provisions for terminating if bronchospasm becomes evident during the procedure. Treatment for airway constriction occurring during the procedure will be given by the physician responsible for the procedure. Administration of inhaled bronchodilator (albuterol) is all that should be required to control the symptoms. You will not be discharged from the EPA Medical Station until your lung function has returned to 80% of your pre-procedure performance. . In the unlikely event that you require additional treatment because the asthma attach continues, you will be transported by ambulance to the emergency room of the UNC Hospital, located 1/4 mile away.

Nose bleeds are another risk of bronchoscopy. This is caused by trauma to the nose during the bronchoscopy procedure. Usually, the bleeding is minor and is

noticed as a few drops of blood in mucous secretions in the nostril. The bleeding usually stops on its own within an hour after the bronchoscopy. On very rare occasions, if the bleeding becomes moderate to severe, your nostril will be packed with sterile gauze to absorb the blood and put pressure on the site of bleeding. Should you require additional treatment, you will be transported to the UNC Hospital Emergency Room. Major nose bleeds during bronchoscopy are very rare and generally limited to persons with kidney disease or a blood clotting disorder. It could also be promoted by chronic use of aspirin (>81 mg), ibuprofen or similar medications. You will not be allowed to participate in this study if you are taking such medications. Therefore the probability of getting a major nose bleed is very small.

Major **bleeding of the airways** is another rare (less than one percent) complication of bronchoscopic procedures. Most episodes of major bleeding due to bronchoscopy occur in persons with underlying predisposing conditions and are due to forceps biopsies of the airways mucosa which will **not** be performed in this study. People who suffer from kidney disease, blood clotting disorders or are chronic users of aspirin-like drugs are at increased risk of bleeding during bronchoscopy. In addition, people with lung cancer or with serious lung infection are more likely to suffer from airway bleeding during bronchoscopy. Your screening medical history, physical examination, and blood analysis will reveal most conditions that would increase your risk of bleeding during the bronchoscopy. You will not be allowed to participate if you have any of these conditions. Therefore your chances of incurring a serious airway bleed during bronchoscopy are extremely small. Nevertheless, if you do experience bleeding during bronchoscopy, you will be under the care of an experienced physician who will take steps to stop the bleeding immediately. A special cart with emergency supplies is available to handle medical emergencies. In the event of a major bleeding episode, you will be immediately transported to the Emergency Room of the UNC Hospital.

Pneumothorax or collapsed lung is another possible complication of bronchoscopic procedures. This complication is more likely to occur during tissue biopsy in the lung periphery, not the major central airways which will be the focus of this study. However you will be advised of the symptoms in the event that you experience a pneumothorax. The symptoms include chest pain and shortness of breath. If you experience these symptoms, you should contact the medical station (966-6232), or page the physician who performed the bronchoscopy. The vast majority of pneumothoraces occur within 24-48 hour of the procedure being completed. While a serious condition, a pneumothorax can be readily treated in an emergency room.

The **lidocaine** used to anesthetize your nasopharynx and reduce your cough can pose certain risks as well. A small fraction of the lidocaine applied to your nose and airways will be absorbed into your bloodstream, where it could cause adverse effects. Your risk of suffering side effects are very small, but would be much greater and potentially life-threatening if you are allergic to lidocaine or other topical anesthetics. You will not be allowed to participate in this study if you have drug allergy to topical anesthetics. When used at high doses, lidocaine can also cause symptoms in your central nervous system (confusion, tremor, euphoria, or,

rarely, seizures) or heart rate disturbances (very fast or very slow heart rate) if an excessive dose of medication is used. Finally, a death in a volunteer receiving an overdose (over 1000 milligrams) of lidocaine during bronchoscopy has been reported from Rochester, New York. However, no serious side effects of this medication have been noted at lower doses such as those described in this protocol which uses up to 360 milligrams of lidocaine during the entire procedure. If any problems develop secondary to the use of lidocaine, the physician bronchoscopist and the doctor on duty that day at the Human Studies Division of the EPA will be available to handle these problems.

Prior to the start of the bronchoscopy **atropine** may be given though a vein in your arm in order to counteract any changes in blood pressure that would result from the placement of the bronchoscope in your airway and to limit the quantity of secretions in your nose and throat. Atropine can cause dry mouth and nose for 30 to 60 minutes after the procedure is completed. This effect should wear off about an hour after the procedure is completed.

Placing an **intravenous catheter** in your arm carries a small risk as well. The needle stick can be momentarily painful and more rarely can leave a bruise in your arm. The medical staff who will be placing the catheter are very experienced and therefore the risk is minimal. Infection is also a very small risk that can result from placing the catheter. Again, the medical staff is very experienced in the use of sterile technique to prevent infection. If you notice redness or swelling in the area surrounding the catheter site, you should contact the medical station at 966-6232 or the physician on call for treatment.

A low grade fever (less than 101EF) during the 24 hours following the procedure occurs in about 25% of patients with respiratory disease undergoing bronchoscopy and BAL. The fever is benign and is usually effectively prevented by administering ibuprofen following the procedure. However, if you experience fever greater than 101 EF or lasting longer than 24 hours you could have pneumonia and should contact the Medical Station immediately so that you can be examined and treated.

Pneumonia occurs in less than 1 percent of patients undergoing bronchoscopy and BAL. Signs of pneumonia include fever greater than 101 EF, or persisting for more than 24 hours, persistent cough with or without sputum production, coughing up blood, chest pain, and shortness of breath or wheeze. Should you experience these symptoms, it is imperative that you contact the Medical Station to be seen and evaluated by a physician. As a routine precaution the Medical Station Staff will contact you between 24 and 48 hours following the procedure to inquire about any symptoms you may be experiencing.

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

There are no risks associated with monitoring your heart by ECG or blood oxygen by pulse oximetry. However, preparing your skin for placement of ECG electrodes and

removing the electrodes may cause some irritation, itching, or burning in some people. If this occurs you should notify the nursing staff.

The following are policies and procedures to minimize risk during the experiment:
1. During this study, skilled personnel, in an adequately equipped facility, will be observing you for any adverse effects. You may, without penalty, stop the test at any time by telling the monitor.
2. A physician will be on call at all times during the study to deal with any medical problems that may arise.
3. Every test has some degree of risk and there may be some risks associated with this experiment which are unforeseeable. You should not participate in the study if you have an acute illness.
4. You may terminate your participation in the experiment at any time and for any reason that you wish without penalty; you will be paid an amount for participation prorated for the time and procedures in which you took part. You understand that you are not under any obligation to complete any test procedures which you find objectionable or uncomfortable.
5. The investigator may terminate your participation in the experiment at any time. If this happens, you will be entitled to full payment for your time commitment and any experimental activities up to that point.
6. Your participation in the study may be postponed if your pre-exposure lung function shows airflow obstruction or if you develop a cold or asthma exacerbation.

What if we learn about new findings or information 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?
You will be given a study code number. All electronic documents will only have that number. The paper records that the coordinators and medical doctors use may have your name. Your information can be linked to your personal information by the study number, however only study personnel have access to your personal information. Paper records that use your name are kept in a locked file cabinet in the EPA Medical Station of the Human Studies Facility. The Medical Station is locked when not attended by study staff, and the EPA Human Studies Facility has limited access to authorized individuals only, 24 hours/day for 7 days/week. Samples used for genetic analysis will be stored at the EPA Human Studies Facility.

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, the U.S. EPA and/or UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by

representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

What will happen if you are injured by this research?

All forms of medical research, diagnosis, and treatment involve some risk of injury or illness. Despite our high level of precaution, you may develop an injury or illness due to participating in this study. If you develop an injury or illness determined by the on duty physician to be due to your participation in this research, the EPA will reimburse your medical expenses to treat the injury or illness up to $5000. If you believe your injury or illness was due to a lack of reasonable care or other negligent action, you have the right to pursue legal remedy. The Federal Tort Claims Act, 28 U.S.C. 2671 et. seq., provides for money damages against the United Sates when personal injury or property loss results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence. If a research related injury or illness occurs, you should contact the Director of the EPA NHEERL Human Research Protocol Office at 919.966.6217.

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

You may withdraw from this study at any time. If you choose to withdraw or are unable to complete the study because of not following the instructions in this consent form, you will receive compensation only for your participation up to that point.

The investigators have the right to stop your participation at any time. This could be because you have had an unexpected reaction, have failed to follow instructions, or because the study has been stopped. After you enroll, if you are dismissed by the investigators before completing the study for reasons that are not your fault, you will be paid for your participation up to that point.

We made need to cancel your study activity due to adverse weather conditions, equipment failure, or other unforeseen events. If a scheduled study activity must be cancelled by the investigators with less than 72 hours prior notice, you will be paid for the time scheduled and cancelled at the standard hourly rate of $12 per hour plus any cancelled activities up to a maximum of $100. When possible, you will be rescheduled at a later time.

Will you receive anything for being in this study?

You will be paid approximately $12 per hour for your participation in this study. Total compensation will be based on the number of exposure sessions that will be required.

1. If you are complete all three exposures sessions of this study, your total compensation including screening will be approximately $2516.

We anticipate performing several tests on you during the course of this study. However, circumstances beyond our control may arise (i.e. equipment failure) which may prevent us from performing a specific test on you. If we are unable to perform a specific test on you which is a primary endpoint for us, you will be compensated for all tests and time completed on that day and rescheduled. If this test is a secondary endpoint for us and is

also a source of compensation, you will be paid for that test, but not rescheduled to make up the procedure.

In addition, you will be reimbursed for reasonable travel expenses and for parking costs while at the research facility. Money received by participants in research studies is normally treated as ordinary income by taxing authorities and we will report payments made to you to the Internal Revenue Service as required by law. This summary is to emphasize the importance of all the visits, and to signify the importance of your time and commitment to the research study. Compensation for the visits will be as follows:

You will be exposed to diesel exhaust ,ozone and have an air control exposure in three separate sessions. Exposure Days 1-2 will be repeated for the second and third chamber exposure session, but a second training Day is not needed. If you complete three exposures, your compensation including the pre-study qualifications and training day will be approximately $2516.

Pre-study qualifications

recruitment screening	$15	Previously paid
physical exam	$15	Previously paid
bronchoscopy physical exam	$20	Previously paid

Pre-study qualification total = $50

Training Day (approximately 2 hours)

Spirometry	$20
Time (2 h @$12/h)	$24

Training Day Total = $ 44

You will be exposed to ozone, diesel exhaust and clean air in separate sessions.

Exposure Day 1 (6 hours)

venipuncture (~80ml, pre)	$ 30 per exposure
Holter monitor	$100 per exposure
chamber exposure (2 hours)	$ 72 per exposure
venipuncture (~80 ml, post)	$ 30 per exposure
spirometry (before and after exposure)	$ 40 per exposure
time (4 h @$12/h)	$ 48 per exposure
Lunch:	$ 5 per exposure

Day 1 total for completion of ONE exposure = $ 325
Day 1 total for completion of TWO exposures = $ 650
Day 1 total for completion of THREE exposures=$975

Exposure Day 2 (4 hours)

Spirometry before bronchoscopy	$ 20 per exposure
venipuncture (~80ml, 24h post)	$ 30 per exposure
time (2h @$12/h)	$ 24 per exposure
Bronchoscopy	$350 per exposure
Endobronchial Brush biopsies	$25 per exposure

Day 2 total for completion of ONE exposure = $449
Day 2 total for completion of TWO exposures = $ 898
Day 2 total for completion of THREE exposures=$1347

Protocol Completion Bonus	**$100**

TOTAL for completion of ONE exposure (excluding Prestudy qualifications and training day)	**$774**
TOTAL for completion of TWO exposures (excluding Prestudy qualifications and training day)	**$1548**
TOTAL for completion of THREE exposures (excluding Prestudy qualifications/training day but including completion bonus)	**$2422**

If you begin but cannot complete the bronchoscopy procedure for voluntary or involuntary reasons, you will receive compensation for your participation up to that point however in you arrive in the lab for the procedure having not followed instructions (eating food, taking NSAIDs or aspirin, or failing to report cold or flu symptoms the day prior to the bronchoscopy) you will be compensated $15 for your time, but will not receive compensation for the bronchoscopy.

You will be asked to bring a lunch for the exposure day and a refrigerator and microwave will be available.

You should understand that your participation is voluntary. You may terminate your participation in the study at any time without penalty. If you voluntarily elect to withdraw from the study at any time or you fail to maintain compliance with eligibility requirements or follow directions of the investigators, you will be paid for that portion of the study that has been completed. In the event a scheduled study activity must be cancelled by the investigators with less than 72 hours prior notice, you will be paid $12 per hour for the time scheduled and cancelled, and 50% of the reimbursement amount for procedures that are canceled up to a total maximum of $100 for all procedures. You will be paid in full for any procedures that may have been started during a current visit if cancelation occurs while you are in the facility. Cancellations could occur due to adverse weather conditions, equipment failure, and other unforeseen events. When feasible,

canceled visits will be rescheduled. 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 you are dismissed by the investigators prior to completion, you will be reimbursed for time and procedures completed up to that point.

Will it cost you anything to be in this study?
There will be no cost to you for participating in the study. However, if you are deemed not eligible to participate in the study for medical reasons, we may suggest that you seek follow-up care from your own health care provider for abnormalities discovered during the screening history, physical examination, or the study. **Such care is entirely at your own expense. EPA will not provide reimbursement for any follow-up care.**

All study procedures will be paid for by the study. We will give you parking coupons to cover the cost of parking. If you live beyond Chapel Hill/Carrboro you will be reimbursed for mileage at the US Government mileage rate in effect at the time.

Who is sponsoring this study?
This research is funded by the United States Environmental Protection Agency. This means that the research team is being compensated by the sponsor for conducting the study. The researchers do not, however, hold a direct financial interest in the sponsor or in the product being studied.

What if you are a UNC student?
You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your class standing or grades at UNC-Chapel Hill. You will not be offered or receive any special consideration if you take part in this research.

What if you are a UNC employee?
Taking part in this research is not a part of your University duties, and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

Who is sponsoring this study?
This research is funded by the US Environmental Protection Agency. This means that the research team is being paid by the sponsor for doing the study.

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 questions, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form.

What if you have questions about your rights as a research subject?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research

subject, you may contact the Chairman of the IRB Committee at 919-966-1344 and /or the Director of the EPA NHEERL Human Research Protocol Office at 919-966-6217.

What specimens will be collected and stored?
Bronchial epithelial cells collected via bronchoscopy and all blood specimens will be stored with your permission. If you agree to have your specimens stored for future research you will need to sign the accompanying consent form ***Consent for Storing Biological Specimens With Identifying Information***.

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IRB Study:# 09-1625

Title of Study: Epigenetic effects of diesel exhaust and ozone exposure

Principal Investigator: Melanie J. Jardim, Ph.D., David Diaz-Sanchez, Ph.D., and Kelly Duncan, Ph.D.

Subject's Agreement to Participate in the Research Study without Genotyping Consent:

I have read the information provided above. I voluntarily **AGREE** to participate in this study and I **REFUSE** to have my provided bronchial epithelial cells genotyped for any genes decided by the study investigators to be related to adverse health effects associated with pollution exposure.

_____ _____

Signature of Research Subject Date

_____

Printed Name of Research Subject

_____ _____

Signature of Person Obtaining Consent Date

_____

Printed Name of Person Obtaining Consent

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