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.

Who is sponsoring this research?
This research is funded by The U.S. Environmental Protection Agency. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this research?
You have the right to ask, and have answered, any questions you may have about this research. If you have questions, 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, anonymously if you wish, the Institutional Review Board at 919-966-3113 or by e-mail to IRB_ subjects@unc.edu.

Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate. I agree to my specimen(s) being stored with the identifying code(s).

_____ _____
Signature of Research Subject Date

_____
Printed Name of Research Subject

_____ _____
Signature of Research Team Member Obtaining Consent Date

_____
Printed Name of Research Team Member Obtaining Consent

THIS CONSENT DOCUMENT WOULD BE USED BETWEEN 9.20.10 AND 9.19.11 BY THE INSTITUTIONAL REVIEW BOARD, UNC-CHAPEL HILL

University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Addendum to provide additional information to subject after original consent

---

IRB Study #_09-1625_____
Consent Form Version Date: ____August 26, 2010_____
Title of Study: Epigenetic effects of diesel exhaust and ozone exposure

Principal Investigator: Melanie J. Jardim, Ph.D.
UNC-Chapel Hill Department: United States Environmental Protection Agency
UNC-Chapel Hill Phone number: 919-966-7320
Email Address:
Co-Investigators: Kelly Duncan
Faculty Advisor: David Diaz-Sanchez, Ph.D.
Funding Source and/or Sponsor: Government

Study Contact telephone number: 919-966-7320
Study Contact email: Jardim.Melanie@epa.gov

The following information should be read as an addition to the original Consent form that you read and signed at the beginning of the study. Unless specifically stated otherwise in the following paragraphs, all information contained in that original Consent Form is still true and remains in effect. Your participation continues to be voluntary. You may refuse to participate, or may withdraw your consent to participate at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your study doctor.

New or additional information

You are being asked to do one additional exposure. The conditions of the exposure and procedures pre- and post-exposure are the same as what are outlined in the original consent form. You will receive compensation for participating in one session:

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

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
Total for Completion of Additional Exposure = $774

If you have any further questions, please call the Director of the NHEERL Human Research Protocol Office at 919-966-6217.

This addendum 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 Chepl Hill. If you have any questions or concerns regarding your rights as a research subject, you may contact

Subject's Agreement:
I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to continue to participate in this research study.

_____ _____
Signature of Research Subject Date

_____
Printed Name of Research Subject

_____ _____
Signature of Research Team Member Obtaining Consent Date

_____
Printed Name of Research Team Member Obtaining Consent

SUBJ #_____ DATE_____

SYMPTOM QUESTIONNAIRE FOR CHAMBER EXPOSURE STUDIES

Pre-Exposure / End Exposure / 24 hrs post end Exposure (Circle one)

INSTRUCTIONS: Please indicate if you are experiencing any of the symptoms or restrictions listed below, using the following scale to indicate the severity. Circle the number.

0 = NONE (not present)
1 = TRACE/NOTICED (barely detectable)
2 = MILD/LIGHT (present, but not annoying)
3 = MODERATE (present, but somewhat annoying)
4 = SEVERE/HEAVY (present and very annoying and painful)

SYMPTOMS	NONE	TRACE	MILD	MODERATE	SEVERE
1. HEADACHE	0	1	2	3	4
2. IRRITATION OF THE NOSE	0	1	2	3	4
3. STUFFY NOSE/SINUS CONGESTION	0	1	2	3	4
4. RUNNY NOSE	0	1	2	3	4
5. DRY/SORE THROAT	0	1	2	3	4
6. PAIN on DEEP INSPIRATION	0	1	2	3	4
7. UNUSUAL FATIGUE OR TIREDNESS	0	1	2	3	4
8. EYE IRRITATION	0	1	2	3	4
9. SHORTNESS OF BREATH	0	1	2	3	4
10. SNEEZING	0	1	2	3	4
11. COUGH	0	1	2	3	4
12. WHEEZING/WHISTLING in CHEST	0	1	2	3	4
13. CHEST TIGHTNESS	0	1	2	3	4
14. SWEATING	0	1	2	3	4
15. Other_____	0	1	2	3	4

APPROVED - IRB UNC-CH
SEP 20 2010

THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
Medical School Building 52
Mason Farm Road
CB #7097
Chapel Hill, NC 27599-7097
(919) 966-3113
Web site: ohre.unc.edu
https://my.research.unc.edu for IRB status
Federalwide Assurance (FWA) #4801

To: Melanie Jardim
Epa
CB: 7315

From: Biomedical IRB

Doug Mann

Authorized signature on behalf of IRB

Approval Date: 11/09/2010
Expiration Date of Approval: 9/19/2011

RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)
Submission Type: Modification
Expedited Category: Minor Change to Previously Approved Research
Study #: 09-1625

Study Title: Epigenetic Effects of Diesel Exhaust and Ozone Exposure
Sponsors: US Environmental Protection Agency - GRANTS

This submission has been approved by the above IRB for the period indicated. It has been determined that the risk involved in this modification is no more than minimal. Unless otherwise noted, regulatory and other findings made previously for this study continue to be applicable.

Submission Description:

This modification, dated November 8, 2010 allows for a single patient to complete an additional exposure to collect lung epithelial cells via bronchoscopy. An addendum has been included.

Investigator's Responsibilities:

When applicable, enclosed are stamped copies of approved consent documents and other recruitment materials. You must copy the stamped consent forms for use with subjects unless you have approval to do otherwise.

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40 CFR 26 (EPA), where applicable.

CC:
David Diaz Sanchez, Environmental Protection Agency
Robert Truckner, (EPA), Non-IRB Review Contact

11/9/10 9/19/11

University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Addendum to provide additional information to subject after original consent

---

IRB Study #_09-1625_____
Consent Form Version Date: ____November 8, 2010_____
Title of Study: Epigenetic effects of diesel exhaust and ozone exposure

Principal Investigator: Melanie J. Jardim, Ph.D.
UNC-Chapel Hill Department: United States Environmental Protection Agency
UNC-Chapel Hill Phone number: 919-966-7320
Email Address:
Co-Investigators: Kelly Duncan
Faculty Advisor: David Diaz-Sanchez, Ph.D.
Funding Source and/or Sponsor: Government

Study Contact telephone number: 919-966-7320
Study Contact email: Jardim.Melanie@epa.gov

The following information should be read as an addition to the original Consent form that you read and signed at the beginning of the study. Unless specifically stated otherwise in the following paragraphs, all information contained in that original Consent Form is still true and remains in effect. Your participation continues to be voluntary. You may refuse to participate, or may withdraw your consent to participate at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your study doctor.

New or additional information

You are being asked to do one additional exposure. The conditions of the exposure and procedures pre- and post-exposure are the same as what are outlined in the original consent form. You will receive compensation for participating in one session:

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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

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
Total for Completion of Additional Exposure = $774

If you have any further questions, please call the Director of the NHEERL Human Research Protocol Office at 919-966-6217.

This addendum 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 Chepl Hill. If you have any questions or concerns regarding your rights as a research subject, you may contact

Subject's Agreement:
I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to continue to participate in this research study.

_____ _____
Signature of Research Subject Date

_____
Printed Name of Research Subject

_____ _____
Signature of Research Team Member Obtaining Consent Date

_____
Printed Name of Research Team Member Obtaining Consent

University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Addendum to provide additional information to subject after original consent

---

IRB Study #_09-1625_____
Consent Form Version Date: ____November 8, 2010_____
Title of Study: Epigenetic effects of diesel exhaust and ozone exposure

Principal Investigator: Melanie J. Jardim, Ph.D.
UNC-Chapel Hill Department: United States Environmental Protection Agency
UNC-Chapel Hill Phone number: 919-966-7320
Email Address:
Co-Investigators: Kelly Duncan
Faculty Advisor: David Diaz-Sanchez, Ph.D.
Funding Source and/or Sponsor: Government

Study Contact telephone number: 919-966-7320
Study Contact email: Jardim.Melanie@epa.gov

The following information should be read as an addition to the original Consent form that you read and signed at the beginning of the study. Unless specifically stated otherwise in the following paragraphs, all information contained in that original Consent Form is still true and remains in effect. Your participation continues to be voluntary. You may refuse to participate, or may withdraw your consent to participate at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your study doctor.

New or additional information

You are being asked to do one additional exposure. The conditions of the exposure and procedures pre- and post-exposure are the same as what are outlined in the original consent form. You will receive compensation for participating in one session:

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chamber exposure (2 hours)	$ 72 per exposure
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Bronchoscopy	$350 per exposure
Endobronchial Brush biopsies	$25 per exposure

Day 2 total for completion of ONE exposure = $449
Total for Completion of Additional Exposure = $774

If you have any further questions, please call the Director of the NHEERL Human Research Protocol Office at 919-966-6217.

This addendum 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 Chepl Hill. If you have any questions or concerns regarding your rights as a research subject, you may contact

Subject's Agreement:
I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to continue to participate in this research study.

_____ _____
Signature of Research Subject Date

_____
Printed Name of Research Subject

_____ _____
Signature of Research Team Member Obtaining Consent Date

_____
Printed Name of Research Team Member Obtaining Consent

THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
Medical School Building 52
Mason Farm Road
CB #7097
Chapel Hill, NC 27599-7097
(919) 966-3113
Web site: ohre.unc.edu
https://my.research.unc.edu for IRB status
Federalwide Assurance (FWA) #4801

To: David Diaz Sanchez
Environmental Protection Agency
7315

From: Biomedical IRB

Authorized signature on behalf of IRB

Approval Date: 1/05/2011
Expiration Date of Approval: 9/19/2011

RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)
Submission Type: Modification
Expedited Category: Minor Change to Previously Approved Research
Study #: 09-1625
Study Title: Epigenetic Effects of Diesel Exhaust and Ozone Exposure
Sponsors: US Environmental Protection Agency - GRANTS

This submission has been approved by the above IRB for the period indicated. It has been determined that the risk involved in this modification is no more than minimal. Unless otherwise noted, regulatory and other findings made previously for this study continue to be applicable.

Submission Description:
This amendment received 12/21/10 addresses personnel updates, including change of PI to David Diaz-Sanchez

Investigator's Responsibilities:
When applicable, enclosed are stamped copies of approved consent documents and other recruitment materials. You must copy the stamped consent forms for use with subjects unless you have approval to do otherwise.

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40 CFR 26 (EPA), where applicable.

CC: Michaekl Schmitt, Environmental Protection Agency; Kelly Duncan, Enviro Med Asthma And Lung Bio; Duncan Kelly; Howard Kehrl, (EPA), Non-IRB Review Contact

OFFICE OF HUMAN RESEARCH ETHICS
Institutional Review Board
MODIFICATION OF APPROVED HUMAN SUBJECTS RESEARCH
Version May 22, 2009

Include the items indicated, where applicable:

- *Check* the relevant items below and include one copy of all checked items 1-5 in the order listed.
- Also include one additional collated set of copies (sorted in the order listed) for items 1 and 2.

→ **Applications will be returned if these instructions are not followed.**

Check	Item	Total No. of Copies
X	1. A concise summary of the requested modification using this form. List and describe each proposed change to aid in IRB review. Add pages as necessary. Provide a concise summary of changes when submitting an updated Investigator Brochure or Master Protocol.	2
□	2. New or revised consent forms, questionnaires, surveys, recruitment materials, advertisements, etc. One copy should have changes highlighted by underlining, and the other clean copy will be used for stamping.	1 highlighted 1 clean
X	3. If you have made substantive changes to the study design or procedures, submit a revised full IRB application with changes highlighted by underlining. If you are making changes only to the first page, just submit that page.	2
□	4. The sponsor's document describing the amendment, if any.	1
	5. If adding personnel, include name, location (UNC or specific outside location), role, and email address for each person who should receive electronic copies of IRB correspondence to PI. For those study personnel *not* in the online UNC-CH ethics training database (http://cfx3.research.unc.edu/training_comp/) include documentation of required training in human research ethics.	1

1 List and describe each proposed change:

This modification is in response to the Biomedical IRB memo dated 12/22/2010 Re: Contingencies to be addressed following IRB review of IRB# 09-1625 Titled: Epigenetic Effects of Diesel Exhaust and Ozone Exposure.

We regret the manner in which we submitted the modification on 12/21/2010. Dr. Melanie Jardim left our organization (USEPA) rather abruptly over the holidays. At this time we request that she be removed as the primary PI on IRB#09-1625. Please remove her from the protocol as the PI of record and replace her with Dr. David Diaz-Sanchez. His contact email is Diaz-Sanchez.David@epa.gov.

Also with this communication, we are designating Michael Schmitt as the official designee of record for IRB#09-1625. He is the current/listed study coordinator for this study. His contact email is Schmitt.mike@epa.gov.

Thank you for your understanding and we apologize for any confusion or inconvenience.

2. Is this modification being submitted in response to an unanticipated problem/adverse event or new findings? ___yes X no

If yes, explain, including whether these events or findings are relevant to participants' willingness to continue.

3. Do any of the proposed changes increase risk? ___yes X_no If yes, explain.

IRB study #: 09-1625 **Date:** 01-03-2011

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

Principal Investigator: David Diaz-Sanchez, Ph.D.

Faculty advisor:

(if applicable)

For industry sponsored research (if applicable):

Sponsor's master protocol version #: Version date:

Investigator Brochure version #: Version date:

Any other details you need documented on IRB approval:

Signature of Principal Investigator or designee — Date: 1/3/10

Signature of Faculty Advisor (if applicable) — Date

OFFICE OF HUMAN RESEARCH ETHICS
Institutional Review Board

APPLICATION FOR IRB APPROVAL OF
HUMAN SUBJECTS RESEARCH
Version June 25, 2009

Part A.1. Contact Information, Agreements, and Signatures

Date: ~~December 21, 2010~~ January 3, 2011

IRB Study #09-1625

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

Name and degrees of Principal Investigator: ~~Melanie J. Jardim, Ph.D.;~~ David Diaz-Sanchez, Ph.D. Kelly Duncan, Ph.D.
Department: US EPA Mailing address/CB #: 104 Mason Farm Road Chapel Hill, NC 27514
UNC-CH PID: ~~71830667~~ 714339670 Pager:
Phone #: 919-966-~~73290676~~ Fax #: 919-966-6271 Email Address: ~~jardim.melanie@epa.gov~~, Diaz-Sanchez.David@epa.gov, Duncan.kelly@epa.gov

For trainee-led projects: __ undergraduate __ graduate _X_ postdoc __ resident __ other
Name of faculty advisor: ~~David Diaz-Sanchez, Ph.D.~~
Department: ~~US Epa~~ Mailing address/CB #: ~~104 Mason Farm Road Chapel Hill, NC 27514~~
Phone #: ~~919-966-0676~~ Fax #: ~~919-966-6271~~ Email Address: ~~diaz-sanchez.david@epa.gov~~

Center, institute, or department in which research is based if other than department(s) listed above:

Name of Project Manager or Study Coordinator (if any): Michael Schmitt, MSPH
Department: US EPA Mailing address/CB #: 104 Mason Farm Road Chapel Hill, NC 27514
Phone #: 919-966-0647 Fax #: 919-966-6271 Email Address: Schmitt.mike@epa.gov

List **all other project personnel** including co-investigators, and anyone else who has contact with subjects or identifiable data from subjects. **Include name, location (UNC or specific outside location), role and email address for each person who should receive electronic copies of IRB correspondence to PI.**

Robert Devlin, PhD.; Heidi Hiers, RN; Maryann Bassett, RN; Martin Case, BS; Andrew Ghio MD; Martha Sue Carraway, MD; Robert Truckner, MD;Howard Kehrl, MD; Tracey Montilla, RN; Michael Schmitt, MS, Sarah Snyder, B.S.; ~~Melanie J. Jardim, Ph.D~~

Name of funding source or sponsor (*please do not abbreviate*):

OFFICE OF HUMAN RESEARCH ETHICS
Institutional Review Board

APPLICATION FOR IRB APPROVAL OF
HUMAN SUBJECTS RESEARCH
Version June 25, 2009

Part A.1. Contact Information, Agreements, and Signatures

Date: January 3, 2011

IRB Study #09-1625

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

Name and degrees of Principal Investigator: David Diaz-Sanchez, Ph.D.; Kelly Duncan, Ph.D.
Department: US EPA Mailing address/CB #: 104 Mason Farm Road Chapel Hill, NC 27514
UNC-CH PID: 714339670 Pager:
Phone #: 919-966-0676 Fax #: 919-966-6271
Email Address: Diaz-Sanchez.David@epa.gov, Duncan.kelly@epa.gov

For trainee-led projects: __ undergraduate __ graduate __ postdoc __ resident __ other
Name of faculty advisor:
Department: Mailing address/CB #:

Phone #: Fax #: Email Address:

Center, institute, or department in which research is based if other than department(s) listed above:

Name of Project Manager or Study Coordinator (if any): Michael Schmitt, MSPH
Department: US EPA Mailing address/CB #: 104 Mason Farm Road Chapel Hill, NC 27514
Phone #: 919-966-0647 Fax #: 919-966-6271 Email Address: Schmitt.mike@epa.gov

List **all other project personnel** including co-investigators, and anyone else who has contact with subjects or identifiable data from subjects. **Include name, location (UNC or specific outside location), role and email address for each person who should receive electronic copies of IRB correspondence to PI.**

Robert Devlin, PhD.; Heidi Hiers, RN; Maryann Bassett, RN; Martin Case, BS; Andrew Ghio MD; Martha Sue Carraway, MD; Robert Truckner, MD;Howard Kehrl, MD; Tracey Montilla, RN; Michael Schmitt, MSPH, Sarah Snyder, B.S.; Melanie J. Jardim, Ph.D

Name of funding source or sponsor (*please do not abbreviate*):

OFFICE OF HUMAN RESEARCH ETHICS
Institutional Review Board

MODIFICATION OF APPROVED HUMAN SUBJECTS RESEARCH

Version May 22, 2009

Include the items indicated, where applicable:

- *Check* the relevant items below and include one copy of all checked items 1-5 in the order listed.
- Also include one additional collated set of copies (sorted in the order listed) for items 1 and 2.

→ **Applications will be returned if these instructions are not followed.**

Check	Item	Total No. of Copies
X	1. A concise summary of the requested modification using this form. List and describe each proposed change to aid in IRB review. Add pages as necessary. Provide a concise summary of changes when submitting an updated Investigator Brochure or Master Protocol.	2
X	2. New or revised consent forms, questionnaires, surveys, recruitment materials, advertisements, etc. One copy should have changes highlighted by underlining, and the other clean copy will be used for stamping.	1 highlighted 1 clean
X	3. If you have made substantive changes to the study design or procedures, submit a revised full IRB application with changes highlighted by underlining. If you are making changes only to the first page, just submit that page.	2
□	4. The sponsor's document describing the amendment, if any.	1
X	5. If adding personnel, include name, location (UNC or specific outside location), role, and email address for each person who should receive electronic copies of IRB correspondence to PI. For those study personnel *not* in the online UNC-CH ethics training database (http://cfx3.research.unc.edu/training_comp/) include documentation of required training in human research ethics.	1

1 List and describe each proposed change:

We submitted a modification on 12/22/10 that was approved on 1/5/11 that changed the PI of record from Melanie Jardim, Ph.D.to David Diaz-Sanchez, Ph.D.. Now we are submitting all three consent forms to clarify and reflect this change as well. We felt a need to clarify the contact information and personnel.

We are also adding an EPA contractor, Kristen Sanders, to the protocol. This individual has successfully completed the CITI training and has been issued a UNC PID number.

2. Is this modification being submitted in response to an unanticipated problem/adverse event or new findings? ___yes _X_no
If yes, explain, including whether these events or findings are relevant to participants' willingness to continue.

3. Do any of the proposed changes increase risk? ___yes _X_no If yes, explain.

IRB study #: #09-1625 **Date:** 1/12/2011

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

Principal Investigator: David Diaz-Sanchez, Ph.D. **Faculty advisor:** (if applicable)

For industry sponsored research (if applicable):

Sponsor's master protocol version #: Version date:
Investigator Brochure version #: Version date:
Any other details you need documented on IRB approval:

for David Diaz-Sanchez 01/12/2011

Signature of Principal Investigator or designee Date

Signature of Faculty Advisor (if applicable) Date

THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
Medical School Building 52
Mason Farm Road
CB #7097
Chapel Hill, NC 27599-7097
(919) 966-3113
Web site: ohre.unc.edu
https://my.research.unc.edu for IRB status
Federalwide Assurance (FWA) #4801

To: David Diaz Sanchez
Environmental Protection Agency
7315

From: Biomedical IRB

Authorized signature on behalf of IRB

Approval Date: 1/13/2011
Expiration Date of Approval: 9/19/2011

RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)
Submission Type: Modification
Expedited Category: Minor Change to Previously Approved Research
Study #: 09-1625
Study Title: Epigenetic Effects of Diesel Exhaust and Ozone Exposure
Sponsors: US Environmental Protection Agency - GRANTS

This submission has been approved by the above IRB for the period indicated. It has been determined that the risk involved in this modification is no more than minimal. Unless otherwise noted, regulatory and other findings made previously for this study continue to be applicable.

Submission Description:
This amendment received 1/12/11 addresses submission of consents with updated personnel & the addition of Kristen Sanders.

Investigator's Responsibilities:
When applicable, enclosed are stamped copies of approved consent documents and other recruitment materials. You must copy the stamped consent forms for use with subjects unless you have approval to do otherwise.

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40 CFR 26 (EPA), where applicable.

CC: Michaekl Schmitt, Environmental Protection Agency; Kelly Duncan, Enviro Med Asthma And Lung Bio; Duncan Kelly; Howard Kehrl, (EPA), Non-IRB Review Contact

THIS CONSENT DOCUMENT SHOULD BE USED ONLY
BETWEEN 1/13/11 AND 9/9/11
APPROVED BY
INSTITUTIONAL REVIEW BOARD, UNC-CHAPEL HILL

University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Addendum to provide additional information to subject after original consent

---

IRB Study #09-1625

Consent Form Version Date: January 12, 2011

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

Principal Investigator: David Diaz-Sanchez, Ph.D.
UNC-Chapel Hill Department: United States Environmental Protection Agency
UNC-Chapel Hill Phone number: 919-966-0676
Email Address: Diaz-Sanchez.David@epa.gov

Co-Investigators: Kelly Duncan, Ph.D. and Mike Schmitt, MSPH
Faculty Advisor:. **Funding Source and/or Sponsor:** Government

Study Coordinator: Mike Schmitt, MSPH
Study Contact telephone number: 919-966-0647
Study Contact email: Schmitt.mike@epa.gov

The following information should be read as an addition to the original Consent form that you read and signed at the beginning of the study. Unless specifically stated otherwise in the following paragraphs, all information contained in that original Consent Form is still true and remains in effect. Your participation continues to be voluntary. You may refuse to participate, or may withdraw your consent to participate at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your study doctor.

New or additional information

You are being asked to do one additional exposure. The conditions of the exposure and procedures pre- and post-exposure are the same as what are outlined in the original consent form. You will receive compensation for participating in one session:

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

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
Total for Completion of Additional Exposure = $774

If you have any further questions, please call the Director of the NHEERL Human Research Protocol Office at 919-966-6217.

This addendum 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

Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to continue to participate in this research study.

_____ _____
Signature of Research Subject Date

_____
Printed Name of Research Subject

_____ _____
Signature of Research Team Member Obtaining Consent Date

_____
Printed Name of Research Team Member Obtaining Consent

THIS CONSENT DOCUMENT SHOULD BE USED ONLY
BETWEEN 1/13/11 AND 9/9/11
APPROVED BY
INSTITUTIONAL REVIEW BOARD OF UNC-CHAPEL HILL

University of North Carolina at Chapel Hill
Consent for Storing Biological Specimens With Identifying Information

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IRB Study # 09-1625

Consent Form Version Date: January 12, 2011

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

Principal Investigator: David Diaz-Sanchez, Ph.D. and Kelly Duncan, Ph.D.
UNC-Chapel Hill Department: US EPA
UNC-Chapel Hill Phone number: 919-966-0676
Email Address: Diaz-Sanchez.David@epa.gov

Co-Investigators: Kelly Duncan, Ph.D. and Mike Schmitt, MSPH
Funding Source and/or Sponsor: EPA funds

Study Coordinator: Mike Schmitt, MSPH
Study Contact telephone number: 919-966-0647
Study Contact email: Schmitt.mike@epa.gov

What are some general things you should know about research?
Research is designed to gain scientific information that may help other people in the future. You may not receive any direct benefit from participating. There also may be risks. You may refuse to take part in research.

Details are discussed below. It is important that you understand this information so that you can make an informed choice. You will be given a copy of this consent form. You should ask the researchers 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 specimen repository or "biobank?"
Research with blood, tissue or body fluids (specimens) can help researchers understand how the human body works. Research can also answer other questions by using specimens. Researchers may develop new tests to find diseases, or new ways to treat diseases. In the future, research may help to develop new products, such as drugs. Specimens are commonly used for genetic research. Sometimes researchers collect and store many specimens together and use them for different kinds of research, or share them with other scientists; this is called a specimen repository or "biobank."

The purpose of this particular repository or biobank is to:

- 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.
- Store samples of respiratory cells and blood samples. These collections are part of the protocol described in the accompanying consent form **Consent to Participate in a Research Study** and the components stored represent excess tissues that are not immediately required for the study but may have value for future research.
- Cells from the lung 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.
- Research reports have suggested that people with particular genes are more susceptible to air pollutants. The epithelial specimens will be genotyped for those specific genes related to adverse health effects of air pollutant exposure.
- Studies of gene expression represent one type of genetic research, thus future investigations involving these specimens are intrinsically of a genetic nature.

All samples will be stored where only project members will have access to the samples. There is a need to store samples in such a repository because this will be an ongoing study where samples from subjects will be collected over an extended period of time. Storing of samples allows for all samples to be processed at the same time and also allows our scientist the opportunity to further study these samples with as yet unknown questions and techniques.

How will the specimens be collected?

Samples will be collected in the following manner.

- Lung cell collection. Cells will be collected from the airways and airspaces of the lung by bronchoscopy with bronchoalveolar lavage and brush biopsy. (This procedure is explained in separate consent.) Fluid will be collected into specimen tubes and placed on ice. The cells will be separated from the fluid by centrifugation (very fast spinning whereby the cells will separate from the liquid and fall to the bottom of the tube), and both samples may be processed immediately, or frozen for later analysis.
- Blood collection. You will have up to 80 cc (about 5 tablespoons) of blood per sample collected from an arm vein by our trained nursing staff. The blood will be placed into specially designed blood collection tubes which allow separation of the fluid and cell portions of blood. Those samples may be processed immediately, or be frozen for later analysis.

What will happen to the specimens?

Samples will be stored at the U.S. Environmental Protection Agency Human Studies Facility located in Chapel Hill, North Carolina. Only project members of the study will have access to the samples. Blood samples will be collected in order to look at but not limited to, indicators of inflammation due to the air pollution exposure. Specimens may be released to other investigators if there is a need to analyze samples with equipment that is not located at our facility.

What are the possible benefits to you?
Benefits to you are unlikely. These studies (current and future) may provide additional information that will be helpful in understanding asthma and how environmental factors affect the disease

What are the possible risks or discomforts involved with the use of your specimens?
This study might involve the following risks and/or discomforts to you:

Risk of breach of confidentiality is minimal. For the mild asthmatic subject, it is conceivable that an employer or insurance company could learn of the diagnosis if you required medical intervention as a result of participating in this study. You will be assigned a study number which will be used for data – not your name. The study number is all that will be entered into computer databases. All paper files which may contain your name or screening number are secure in the EPA building which has limited access 24 hours/day. A numeric coding system will be used to ensure that you cannot be directly identified from the samples alone.

Will there be any cost to you for storage of the specimens?
There will be no cost to you for the storage and use of the specimens for research purposes.

Will you receive anything for the use of your specimens?
You will not receive anything for taking part in this research.

Who owns the specimens?
Any blood, body fluids, or tissue specimens obtained for the purpose of this study become the exclusive property of The U.S. Environmental Protection Agency. The researchers may retain, preserve or dispose of these specimens and may use these specimens for research that may result in commercial applications. There are no plans to compensate you for any future commercial use of these specimens.

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 which 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.
Research studies may be done at many places at the same time. Your personal identifying information will not be sent to outside researchers.

No one 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, 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.

You will not be identified in any report or publication about research using your specimens. 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-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

A Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

Will researchers seek approval from you to do future studies involving the specimens?
By signing this consent form, you are giving your permission for researchers to use your specimens as described above. Current and future research is overseen by a committee called the Institutional Review Board (IRB). The role of the IRB is to protect the rights and welfare of research participants. In some cases, the IRB may require that you be re-contacted and asked for your consent to use your specimens in a specific research study. You have the right, at that future time, not to participate in any research study for which your consent is sought. Refusal to participate will not affect your medical care or result in loss of benefits to which you are entitled.

Will you receive results from research involving your specimens?
Most research with your specimens is not expected to yield new information that would be meaningful to share with you personally. There are no plans to re-contact you or other subjects with information about research results.

Can you withdraw the specimens from the research repository?
If you decide that you no longer wish for the specimens to be stored, you should contact the researchers on the front page of this form. It is best to make your request in writing.

Any analysis in progress at the time of your request or already performed prior to your request being received by the researcher will continue to be used as part of the research study. Once the researchers have been notified, your remaining specimens would be destroyed. If you do not make such a request, the specimens may be stored forever. The researchers may choose to destroy the specimens at any time.

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.

Who is sponsoring this research?

This research is funded by The U.S. Environmental Protection Agency. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this research?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions, 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, anonymously if you wish, the Institutional Review Board at 919-966-3113 or by e-mail to IRB_ subjects@unc.edu.

Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate. I agree to my specimen(s) being stored with the identifying code(s).

_____ _____

Signature of Research Subject Date

_____

Printed Name of Research Subject

_____ _____

Signature of Research Team Member Obtaining Consent Date

_____

Printed Name of Research Team Member Obtaining Consent

THIS CONSENT DOCUMENT SHOULD BE USED ONLY
BETWEEN 1/13/11 AND 9/19/11
APPROVED BY
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: January 12, 2011

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

Principal Investigator: David Diaz-Sanchez, Ph.D. and Kelly Duncan, Ph.D.
Department: United States Environmental Protection Agency
Phone number: 919-966-0676

Study Coordinator: Michael T. Schmitt, MSPH
Phone: 919-966-0647
Schmitt.mike@epa.gov

Other Contact Information: Kelly Duncan, Ph.D.
Phone: 919-966-5445
Duncan.kelly@epa.gov

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 With 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.

Are there any reasons you should not participate?

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 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 fiber optic 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 fiber optic 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 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 mg 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, and 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** those 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 is 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 that 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***.

- -

IRB Study: # 09-1625

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

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

Subject's Agreement to Participate in the Research Study *with* Genotyping Consent:

I have read the information provided above. I voluntarily **AGREE** to participate in this study and I voluntarily **AGREE** 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.

Signing here and agreeing to participate in this study DOES NOT allow us to store your samples.

Signature of Research Subject ______________________ Date ____________

Printed Name of Research Subject ______________________

Signature of Person Obtaining Consent ______________________ Date ____________

Printed Name of Person Obtaining Consent ______________________

- -

IRB Study: # 09-1625

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

Principal Investigator: 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 ____________________

- -

IRB Notice
IRB
to:
diazsanchez.david
03/25/2011 09:24 AM
Cc:
Mike Schmitt, Kelly Duncan, Kelly Duncan, Howard Kehrl
Show Details

To: David Diaz Sanchez
Environmental Protection Agency
7315

From: Biomedical IRB

Approval Date: 3/24/2011
Expiration Date of Approval: 9/19/2011

RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)
Submission Type: Modification
Expedited Category: Minor Change to Previously Approved Research
Study #: 09-1625
Study Title: Epigenetic Effects of Diesel Exhaust and Ozone Exposure
Sponsors: US Environmental Protection Agency - GRANTS

This submission has been approved by the above IRB for the period indicated. It has been determined that the risk involved in this modification is no more than minimal. Unless otherwise noted, regulatory and other findings made previously for this study continue to be applicable.

Submission Description:
This amendment received 3/23/11 addresses editorial and clarifying revisions along with dropping the diesel arm of this study, but those currently consented/enrolled and scheduled for the 7 visits will proceed with all exposures.

Investigator's Responsibilities:
IF YOU SUBMITTED ON PAPER, enclosed are stamped copies of approved consent documents and other recruitment materials (when applicable). You must copy the stamped consent forms for use with subjects unless you have approval to do otherwise.
This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40 CFR 26 (EPA), where applicable.

CC: Michaekl Schmitt, Environmental Protection Agency; Kelly Duncan, Enviro Med Asthma And Lung Bio
Duncan Kelly; Howard Kehrl, (EPA), Non-IRB Review Contact

IRB Informational Message—please do not use email REPLY to this address

OFFICE OF HUMAN RESEARCH ETHICS
Institutional Review Board
MODIFICATION OF APPROVED HUMAN SUBJECTS RESEARCH
Version May 22, 2009

Include the items indicated, where applicable:

- *Check* the relevant items below and include one copy of all checked items 1-5 in the order listed.
- Also include one additional collated set of copies (sorted in the order listed) for items 1 and 2.

→ **Applications will be returned if these instructions are not followed.**

Check	Item	Total No. of Copies
X	1. A concise summary of the requested modification using this form. List and describe each proposed change to aid in IRB review. Add pages as necessary. Provide a concise summary of changes when submitting an updated Investigator Brochure or Master Protocol.	2
X	2. New or revised consent forms, questionnaires, surveys, recruitment materials, advertisements, etc. One copy should have changes highlighted by underlining, and the other clean copy will be used for stamping.	1 highlighted 1 clean
□	3. If you have made substantive changes to the study design or procedures, submit a revised full IRB application with changes highlighted by underlining. If you are making changes only to the first page, just submit that page.	2
□	4. The sponsor's document describing the amendment, if any.	1
□	5. If adding personnel, include name, location (UNC or specific outside location), role, and email address for each person who should receive electronic copies of IRB correspondence to PI. For those study personnel *not* in the online UNC-CH ethics training database (http://cfx3.research.unc.edu/training_comp/) include documentation of required training in human research ethics.	1

1 List and describe each proposed change:

After reviewing the data collected to date for the diesel exposure, we have decided to drop the diesel arm of this study going forward. We have an adequate amount of data collected and believe by doing more diesel exposures we would not significantly alter the results. However, those subjects currently consented/enrolled and scheduled for the 7 visits, which include the diesel arm, will proceed with all the exposures. This will mean that the last diesel exposure will occur on 5/16/2011.

We will continue this study as a two arm study (ozone, clean air) by modifying our consent and recruiting/enrolling all future subjects in only 2 arms of this study (clean air and ozone).

We have also cleaned up the document by minor editorial revisions allowing for better clarity when reading the document, these include but not limited to spelling and grammar.

2. Is this modification being submitted in response to an unanticipated problem/adverse event or new findings? ___yes _X__no
If yes, explain, including whether these events or findings are relevant to participants' willingness to continue.

3. Do any of the proposed changes increase risk? ___yes _X__no If yes, explain.

IRB study #: 09-1625 **Date:** 3-23-2011

THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
Medical School Building 52
Mason Farm Road
CB #7097
Chapel Hill, NC 27599-7097
(919) 966-3113
Web site: ohre.unc.edu
https://my.research.unc.edu for IRB status
Federalwide Assurance (FWA) #4801

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Duncan Kelly; Howard Kehrl, (EPA), Non-IRB Review Contact

Epigenetic Effects of Diesel Exhaust and Ozone Exposure, IRB Study #09-1625
Web Site Announcement
www.epastudies.org

APPROVED - IRB UNC-CH
MAR 24 2011

LAMARCK

What is the purpose of the research study?

The purpose of this research study is to compare changes in lung function, lung cells, blood and heart rate between people with and without asthma when they are exposed to clean air and ozone. This study is for healthy people who have mild to moderate asthma and those who do not have asthma.

Can I take part in the study?
You may be able to be in the study if you

- Are between 18 and 55 and
- Are healthy or
- Are healthy but have mild to moderate asthma and
- Do not smoke and
- Can perform moderate exercise and
- Can stop taking certain drugs and food supplements for a week before each exposure

What will I be asked to do?

- Have a free physical exam
- Have blood drawn
- Take part in breathing tests, including spirometry (explanation link provided)
- Have your heart rate monitored (explanation link provided)
- Have your blood pressure monitored
- Use an exercise bike during testing
- Come in 2 different times for 2 hour exposure sessions when you will either
  - Breathe clean air, or
  - Breathe air polluted with carefully controlled amount of ozone
- Return the next day for bronchoscopy (explanation link provided) and more testing

How long will it take?

- After 2 screening visits there will be 5 study visits, including 1 training visit and 2 sets of 2-day exposure visits, each set separated by at least 4 weeks
- In total, the study will take about 22 hours over 6 to 8 weeks.

What will I get for volunteering?

- You will be paid for screening, for the study, and for out of town travel.

How can I sign up or get more information?
Call or send an email (link provided)l. Our office hours are Monday-Friday from 8 am to 5 pm EST. After hours please leave a message on voice mail, and we will return your call promptly.

- (919 966-0604 (local)
- 1-888-279-9353 (toll free)
- recruitment@epa.gov

Advertising: Epigenetic effects of diesel exhaust and ozone exposure.

The US Environmental Protection Agency is seeking

Adults With Asthma

For Research Study

Do you have asthma or think you have asthma?
Are you between 18 and 55?

This is an air pollution study about clean air & ozone. It requires screening plus 5 visits over about 6 to 8 weeks and includes two 2-day exposure sessions with exercise.

919-966-0604 or **1-888-279-9353**
www.epastudies.org

The Human Studies Facility is located on the UNC-CH campus

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MAR 24 2011

Advertising: Epigenetic effects of diesel exhaust and ozone exposure.

The US Environmental Protection Agency is seeking

Adult Volunteers

For Research Study

Now recruiting healthy adults with and without asthma ages 18 to 55 for an air pollution study about clean air & ozone. Study requires screening plus 5 visits over about 6 to 8 weeks. Includes two 2-day exposure sessions with exercise.

919-966-0604 or **1-888-279-9353**
www.epastudies.org

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Recruitment Script

IRB Study # 09-1625

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MAR 24 2011

Title: Epigenetic effects of diesel exhaust and ozone exposure (Lamarck)

Purpose:
The purpose of this research study is to compare changes in lung function, lung cells, blood and heart rate between people with and without asthma when they are exposed to clean air and ozone. This study is for healthy people ages 18 to 55 who have mild to moderate asthma and those who do not have asthma.

Procedures and Payment:

The study will require two screening visits to the EPA Human Studies Facility (one to complete medical history paperwork, and the other for a physical exam), followed by a training session and two 2-day exposure sessions, each separated by at least four weeks. On the second day of each exposure session volunteers will have a bronchoscopy, a procedure used to get a lung cell sample. During the procedure, a doctor passes a thin tube through your nose and throat into the airways. Cells are removed either by a squirt of salt water or a gentle brushing. Before inserting the tube, the doctor will give you anesthetic to numb your nose and throat. You will be given an intravenous (IV) line. After the procedure, nurses will monitor your heart rate and blood pressure. The bronchoscopy itself usually lasts about 30 minutes, but the entire procedure, including preparation and recovery time, takes about 4 hours, and we ask that you stay in the Chapel Hill area for 48 hours afterward.

Training takes about 2 hours. Each exposure day takes about 6 hours and the follow up day takes 4. During exposure sessions you will be asked to give blood samples, ride an exercise bike, and perform several different breathing tests. You will also wear a heart monitor during the study sessions and over night. The total amount of time is about 22 hours over about 6 to 8 weeks. Each set of exposures is separated by 4 weeks.

If you complete the screening visits, the training visit, and both 2-day study sessions, you will be paid $1742.

Study Schedule

Screening, 2 visits, as needed: 3 hours

Training visit, *days & times to be decided*: 2 hours

Session 1, Day 1, 8 AM, *days to be decided*: 6 hours

Session 1, Day 2, 8 AM, day after Day 1, 4 hours

Does this seem like something that interests you?

Study Restrictions:
In addition to meeting all study eligibility criteria (*see IRB application*), volunteers must be willing to adhere to the following restrictions as well:

- No over the counter pain medications such as aspirin, Advil, Aleve, or other non-steroidal anti-inflammatory medications for 7 days prior to all visits. Tylenol is permitted.
- No vitamins or multivitamins with C or E and no fish oil supplements for 7 days prior to each visit.
- No antihistamines for 7 days before all visits.
- No smoke and fumes for 24 hours before all visits
- No drinking alcohol 24 hours before all visits
- No strenuous exercise for 24 hours prior to and after all visits
- No caffeine for 12 hours before to all study visits.
- No inhaled bronchodilators for 12 hours prior to bronchoscopy
- Nothing to eat or drink after midnight the evening before the bronchoscopy (Exposure Day 2)

APPROVED - TRB. UNC-CH
MAR 24 2011

LAMARCK Study E-mail Announcement

SUBJECT: INFORMATIONAL: Research Study about Ozone and Exercise for People With and Without Asthma

This research study is for healthy non-smoking people between 18 and 55 who have mild to moderate asthma, and others who do not have asthma. The purpose of the study is to compare changes in lung function, lung cells, blood and heart rate between people with and without asthma when they are exposed to clean air and ozone. The study involves 5 visits after screening over about 6 to 8 weeks. It requires a commitment of about ~~32~~ 22 hours, including 2 2-day exposure sessions. You will be paid for screening and the study. Please visit **www.epastudies.org** for more information or call the Westat EPA Recruiting Office at 919-966-0604.

Approved [date], by the Office of Human Research Ethics Biomedical Institutional Review Board. IRB # 09-1625: Epigenetic effects of diesel exhaust and ozone exposure.

This email is sponsored by: U.S. Environmental Protection Agency Human Studies Division, located on the UNC-Chapel Hill campus.

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE 3/24/11 9/19/11

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: March 23, 2011
Title of Study: Epigenetic effects of diesel exhaust and ozone exposure

Principal Investigator: David Diaz-Sanchez, Ph.D. and Kelly Duncan, Ph.D.
Department: United States Environmental Protection Agency
Phone number: 919-966-0676

Study Coordinator: Michael T. Schmitt, MSPH
Phone: 919-966-0647
Schmitt.mike@epa.gov

Other Contact Information: Kelly Duncan, Ph.D.
Phone: 919-966-5445
Duncan.kelly@epa.gov

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 clean air 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 With 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.

Are there any reasons you should not participate?

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 7 visits to the research facility over approximately 3-4 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 minute ventilation normalized for body surface of 25L/min/m^2BSA 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 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 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 fiber optic 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 fiber optic tube that is about two feet 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. You will be instructed not to eat or drink anything after midnight. 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 be 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 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 cannulawill 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 may repeat the spirometry lung function test if the physician deems it necessary. 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 mg 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 sign the section under ***Subject's Agreement to Participate in the Research Study Without Genotyping Consent*** 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. With your permission, we will continue to store any samples that we collect and possibly use them for other studies. You will be given a separate consent form for this storage but you do not have to allow your samples to be stored indefinitely in order to participate in this study. 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, and 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 air pollution. 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. However, if possible, we may chose to use a different chamber, one which is as large as a full size living room and has a separate (private) bathroom inside.

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** those 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 is 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 that 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 complete both exposure sessions of this study, your total compensation including screening will be approximately $1742

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 ozone and have an air control exposure in two separate sessions. Exposure Days 1-2 will be repeated for the second chamber exposure session, but a second training day is not needed. If you complete both exposures, your compensation including the pre-study qualifications and training day will be approximately $1742

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 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

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

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 but including completion bonus)	**$1648**

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.

<u>What specimens will be collected and stored?</u>
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 <u>With</u> Identifying Information***.

- -

IRB Study: # 09-1625

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

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

<u>Subject's Agreement to Participate in the Research Study *with* Genotyping Consent:</u>

I have read the information provided above. I voluntarily **AGREE** to participate in this study and I voluntarily **AGREE** 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

- -

IRB Study: # 09-1625

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

Principal Investigator: 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	

IRB Notice
IRB
to:
David Diaz-Sanchez
06/22/2011 02:49 PM
Cc:
Mike Schmitt, Kelly Duncan, Kelly Duncan, Howard Kehrl
Show Details

To: David Diaz Sanchez
Environmental Protection Agency
7315

From: Biomedical IRB

Approval Date: 6/22/2011
Expiration Date of Approval: 9/19/2011

RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)
Submission Type: Modification
Expedited Category: Minor Change to Previously Approved Research
Study #: 09-1625

Study Title: Epigenetic Effects of Diesel Exhaust and Ozone Exposure
Sponsors: US Environmental Protection Agency - GRANTS

This submission has been approved by the above IRB for the period indicated. It has been determined that the risk involved in this modification is no more than minimal. Unless otherwise noted, regulatory and other findings made previously for this study continue to be applicable.

Submission Description:

This modification, dated June 16, 2011 adds non-radioactive heavy isotope of oxygen to generate ozone for both in vivo and in vitro exposures. An additional 15 healthy volunteers will be recruited for this purpose. The bronchoscopy will be performed 1 hour post exposure instead of 18 hours. Finally, an additional 20 subject will be enrolled into the main arm of the study.

Investigator's Responsibilities:

IF YOU SUBMITTED ON PAPER, enclosed are stamped copies of approved consent documents and other recruitment materials (when applicable). You must copy the stamped consent forms for use with subjects unless you have approval to do otherwise. **IF YOU SUBMITTED ONLINE (Behavioral and Public Health-Nursing IRBs Only),** your approved consent forms and other documents are available online at http://apps.research.unc.edu.

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40 CFR 26 (EPA), where applicable.

CC:
Michaekl Schmitt, Environmental Protection Agency
Kelly Duncan, Enviro Med Asthma And Lung Bio
Duncan Kelly
Howard Kehrl, (EPA), Non-IRB Review Contact

IRB Informational Message—please do not use email REPLY to this address

THE UNIVERSITY
OF NORTH CAROLINA
AT CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
Medical School Building 52
Mason Farm Road
CB #7097
Chapel Hill, NC 27599-7097
(919) 966-3113
Web site: ohre.unc.edu
https://my.research.unc.edu for IRB status
Federalwide Assurance (FWA) #4801

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CC:
Michaekl Schmitt, Environmental Protection Agency
Kelly Duncan, Enviro Med Asthma And Lung Bio
Duncan Kelly

Howard Kehrl, (EPA), Non-IRB Review Contact

Recruitment Script

APPROVED - IRB, UNC-CH

JUN 22 2011

IRB Study # 09-1625

Title: Epigenetic effects of diesel exhaust and ozone exposure (LAMARCK 18 portion of the study)

Purpose:
The purpose of the LAMARCK research study is to compare changes in lung function, lung cells, blood and heart rate between people with and without asthma when they are exposed to clean air and ozone. The purpose of this part of the study, called LAMARCK 18, is to measure the amount of ozone that attaches to your lung cells. This study is for healthy people ages 18 to 55 who do not have asthma, and who have previously undergone bronchoscopy at the EPA Human Studies Facility.

EPA investigators will expose volunteers to a type of ozone, called 18Ozone, which can be detected in cells. This 18Ozone is heavier but otherwise exactly the same as regular ozone and has the same effects, so there is no additional risk.

Procedures:
If your EPA screening is up to date, the study will require a training session that takes about 2 hours, and one exposure session followed an hour later by bronchoscopy. The exposure day with bronchoscopy takes about 6 hours. During the exposure session you will be asked to give blood samples, ride an exercise bike, and perform several different breathing tests. As with your previous bronchoscopy at EPA, you must not eat or drink anything after midnight the day of the study, and we ask that you stay in the Chapel Hill area for 48 hours afterward.

Unlike other exercise studies at EPA, you must arrive fasting – nothing to eat or drink after midnight – and you should be aware that you will not be allowed fluids while exercising. You will be given sips of water and food about 1 ½ hours after the bronchoscopy procedure is complete in the afternoon.

Payment:
If you complete the training visit, and exposure session and bronchoscopy, you will be paid $561.

Study Schedule

Training visit, *days & times to be decided*: 2 hours
Exposure & Bronchoscopy, 8 AM, days to be decided: 6 hours.

Does this seem like something that interests you?

Study Restrictions:

In addition to meeting all study eligibility criteria (*see IRB application*); volunteers must be willing to adhere to the following restrictions as well:

- No over the counter pain medications such as aspirin, Advil, Aleve, or other non-steroidal anti-inflammatory medications for 7 days prior to all visits. Tylenol is permitted.
- No vitamins or multivitamins with C or E and no fish oil supplements for 7 days prior to each visit.
- No antihistamines for 7 days before all visits.
- No smoke and fumes for 24 hours before all visits
- No drinking alcohol 24 hours before all visits
- No strenuous exercise for 24 hours prior to and after all visits
- No caffeine for 12 hours before to all study visits.
- Nothing to eat or drink after midnight the evening before the study

THIS CONSENT DOCUMENT SHOULD BE USED ONLY
BETWEEN 10/22/11 AND 9/19/11
APPROVED BY
INSTITUTIONAL REVIEW BOARD, UNC-CHAPEL HILL

University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Addendum to measure the exact amount of ozone delivered to the lungs in IRB#09-1625.

Subjects 18 years of age or older
Biomedical Form

IRB Study: # 09-1625

Consent Form Version Date: June 16, 2011
Title of Study: Epigenetic effects of diesel exhaust and ozone exposure

Principal Investigator: David Diaz-Sanchez, Ph.D. and Kelly Duncan, Ph.D.
Department: United States Environmental Protection Agency
Phone number: 919-966-0676

Study Coordinator: Michael T. Schmitt, MSPH
Phone: 919-966-0647
Schmitt.mike@epa.gov

Other Contact Information: Kelly Duncan, Ph.D.
Phone: 919-966-5445
Duncan.kelly@epa.gov

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 measure the amount of ozone that attaches to your lung cells. We will expose you to a type of ozone (18Ozone) which is not radioactive but we can detect in cells using special instruments. This 18Ozone is heavier but otherwise exactly the same as regular ozone and has the same effects, so there is no additional risk. This heavier type of ozone is naturally present in the atmosphere at low levels. We have successfully exposed volunteers to 18ozone in a previous study done in our facility in 1993. We will look for the 18Ozone in your lung cells by conducting a bronchoscopy about an hour after the exposure and also obtain a small amount of blood (about 2 tablespoons) to determine how much 18Ozone may have left the lung.

- 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 With Identifying Information.***

Are there any reasons you should not participate?

You should not participate in this study if:

- You have not already successfully completed a bronchoscopy in our facility.
- You are uncomfortable in small, enclosed spaces. The exposure chamber itself is approximately 4 x 8 x 6 feet in size.
- You are pregnant, attempting to become pregnant or nursing an infant
- You have a history of significant chronic illness.
- 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 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 week 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 prior to the exposure day because of the bronchoscopy.
- 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 15 subjects in this research study.

How long will your participation last?

Your participation in this study may require up to 3 visits to the research facility over approximately 1-2 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 minute ventilation normalized for body surface of 25L/min/m^2BSA will be determined

Exposure Day: You will be asked to refrain from eating or drinking anything after midnight and should arrive at the EPA medical station no later than 8 am. You will need to wear comfortable clothes and shoes.

Prior to exposure, you will:

- Have your vital signs checked (heart rate, respiratory rate, blood pressure, oxygen saturation level). Have a pregnancy test if applicable.
- 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 monitors placed on you so that we can watch your heart rate and rhythm while you are in our facility.
- 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 to 18ozone. The amount of ozone you will be exposed to is less than what you would likely encounter over 24 hours on a smoggy day in an urban area. There is no additional risk to you during the inhalation of 18ozone. This isotope is naturally present in the atmosphere at low levels. We have successfully exposed volunteers to 18ozone in a previous study done in our facility in 1993. The exposure chamber is 4 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. We will compare the results of this breathing test with the one you performed prior

to ozone to make sure that your ability to blow out air (a measure of how well your lungs are functioning) very quickly was not decreased so much during the ozone exposure that it would be risky to perform bronchoscopy on you (exposure to ozone can affect this function in some people). We may ask you to remain in our facility for a while to see if your ability to blow out air very quickly (change in FEV1) improves (which it does in most people) and may give you some medication to reverse the effects of ozone. However, if your FEV1 remains low, we may opt to not perform the bronchoscopy on you. In this case you would be paid for the entire procedure.

- Have your vital signs checked.
- Have up to 20 mL blood drawn (about 2 tablespoons). We will test this blood to see if 18ozone was attached to any of your blood cells.
- Approximately one hour after exposure you will undergo a bronchoscopy. 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 fiber optic 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 pollutant exposure. The bronchoscope is a flexible fiber optic tube that is about two feet 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 have this procedure about an hour after your 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. 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. 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 be 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 wall of the airway several times. Up to 8 brush biopsies are taken.

Bronchoalveolar Lavage (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 cannula 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 eat 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 may repeat the spirometry lung function test if the physician deems it necessary. You will be discharged if your vital signs are stable, chest examination is normal. Prior to discharge you will be medicated with 600 mg 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. 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.

You should not participate in this study if you are unwilling or unable to remain in the local area for 24 hours following the bronchoscopy

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. With your permission, we will continue to store any samples that we collect and possibly use them for other studies. You will be given a separate consent form for this storage but you do not have to allow your samples to be stored indefinitely in order to participate in this study. 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. The ozone used in this exposure will be generated using the non-radioactive heavier version of oxygen (18O). The amount of ozone you will be exposed to is less than what you would likely encounter over 24 hours on a smoggy day in an urban area. There is no additional risk to you during the inhalation of 18ozone. It's naturally present in the atmosphere at low levels. We have successfully exposed volunteers to 18ozone in a previous study done in our facility in 1993. During ozone exposure, you may experience some minor degree of airway irritation, cough, and shortness of breath or wheezing. 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.

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 of the bronchoscopy procedure 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 be cancelled.

A second risk of bronchoscopy is **coughing** that result 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.

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 bronchoscopy 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 bronchoscopy 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 is 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. Additionally note that a death occurred in a volunteer receiving an overdose (over 1000 milligrams) of lidocaine during a bronchoscopy in a study out of 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 Environmental Public Human 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 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, however, 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 101°F) 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°F 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°F, 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.

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.

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, and will also be compensated for having blood taken as well as undergoing bronchoscopy.

1. If you complete this study, the total

   compensation excluding screening will be approximately $561

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:

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

Exposure Day (approximately 6 hours)

venipuncture (~20 ml, post)	$ 30
spirometry (before and after exposure)	$ 40
time (6 h @$12/h)	$ 72
Bronchoscopy	$350
Endobronchial Brush biopsies	$25

Total for completion of Exposure Day = $517

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 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 exposure or bronchoscopy. 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: David Diaz-Sanchez, Ph.D., and Kelly Duncan, Ph.D.

Subject's Agreement to Participate in the Research Study

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

______________________________	______________
Signature of Research Subject	Date
______________________________	
Printed Name of Research Subject	
______________________________	______________
Signature of Person Obtaining Consent	Date
______________________________	
Printed Name of Person Obtaining Consent	

- -

OFFICE OF HUMAN RESEARCH ETHICS
Institutional Review Board

APPLICATION FOR IRB APPROVAL OF
HUMAN SUBJECTS RESEARCH
Version June 25, 2009

Part A.1. Contact Information, Agreements, and Signatures

Date: June 16, 2011

IRB Study #09-1625

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

Name and degrees of Principal Investigator: David Diaz-Sanchez, Ph.D.; Kelly Duncan, Ph.D.
Department: US EPA Mailing address/CB #: 104 Mason Farm Road Chapel Hill, NC 27514

UNC-CH PID: 714339670 Pager:
Phone #: 919-966-0676 Fax #: 919-966-6271
Email Address: Diaz-Sanchez.David@epa.gov, Duncan.kelly@epa.gov

For trainee-led projects: __ undergraduate __ graduate __ postdoc __ resident __ other
Name of faculty advisor:
Department: Mailing address/CB #:

Phone #: Fax #: Email Address:

Center, institute, or department in which research is based if other than department(s) listed above:

Name of Project Manager or Study Coordinator (if any): Michael Schmitt, MSPH
Department: US EPA Mailing address/CB #: 104 Mason Farm Road Chapel Hill, NC 27514
Phone #: 919-966-0647 Fax #: 919-966-6271 Email Address: Schmitt.mike@epa.gov

List **all other project personnel** including co-investigators, and anyone else who has contact with subjects or identifiable data from subjects. **Include name, location (UNC or specific outside location), role and email address for each person who should receive electronic copies of IRB correspondence to PI.**

Robert Devlin, PhD.; Heidi Hiers, RN; Maryann Bassett, RN; Martin Case, BS; Andrew Ghio MD; Martha Sue Carraway, MD; Robert Truckner, MD;Howard Kehrl, MD; Tracey Montilla, RN; Michael Schmitt, MSPH, Sarah Snyder, B.S.; Melanie J. Jardim, Ph.D, Kristen Sanders, B.S.

Name of funding source or sponsor (*please do not abbreviate*):
__ not funded _X_ Federal __ State __ industry __ foundation __ UNC-CH
__ other (specify):

For external funding, RAMSeS proposal number (from Office of Sponsored Research): The PI is a USEPA scientist and this project is being funded by intramural EPA funds

For industry sponsored research (if applicable):

Sponsor's master protocol version #: Version date:

Investigator Brochure version #: Version date:

Any other details you need documented on IRB approval:

Checklist of Items to Include with Your Submission

Include the following items with your submission, where applicable.

- Check the relevant items below and include one copy of all checked items 1-11 in the order listed.
- Also include two additional collated sets of copies (sorted in the order listed) for items 1-7.

Applications must "stand alone" and should provide all information requested, i.e., complete answers must be contained in the application. While you may reference other documents with supporting information, do not respond solely by stating "see attached."

Applications will be returned if these instructions are not followed.

Check	Item	Total No. of Copies
□	1. This application. One copy must have original PI signatures.	3
□	2. Consent and assent forms (include DHHS-approved sample, when one exists), fact or information sheets, phone and verbal consent scripts.	3
□	3. HIPAA authorization addendum to consent form.	3
□	4. All recruitment materials including final copies of printed advertisements, audio/video taped advertisements, scripts, flyers, letters, and emails.	3
□	5. Questionnaires, focus group guides, scripts used to guide phone or in-person interviews, etc.	3
□	6. Documentation of reviews from any other committees (e.g., Clinical and Translational Research Center (CTRC), Oncology Protocol Review Committee, or local review committees in Academic Affairs).	3
□	7. Protocol, grant application or proposal supporting this submission, if any (e.g., extramural grant application to NIH or foundation, industry protocol, student proposal). This must be submitted if an external funding source or sponsor is checked on the previous page.	1
□	8. Addendum for Multi-Site Studies where UNC-CH is the Lead Coordinating Center.	1
□	9. Data use agreements (may be required for use of existing data from third parties).	1
□	10. Only for those study personnel *not* in the online UNC-CH human research ethics training database (http://cfx3.research.unc.edu/training_comp/): Documentation of required training in human research ethics.	1
□	11. For drug studies, Investigator Brochure if one exists. If none, include package insert for previously approved uses..	1

Principal Investigator: I will personally conduct or supervise this research study. I will ensure that this study is performed in compliance with all applicable laws, regulations and University policies regarding human subjects research. I will obtain IRB approval before making any changes or additions to the project. I will notify the IRB of any other changes in the information provided in this application. I will provide progress reports to the IRB at least annually, or as requested. I will report promptly to the IRB all unanticipated problems or serious adverse events involving risk to human subjects. I will follow the IRB approved consent process for all subjects. I will ensure that all collaborators, students and employees assisting in this research study are informed about these obligations. All information given in this form is accurate and complete.

_____ _____

Signature of Principal Investigator Date

Faculty Advisor if PI is a Student or Trainee Investigator: I accept ultimate responsibility for ensuring that this study complies with all the obligations listed above for the PI.

_____ _____

Signature of Faculty Advisor Date

Note: The following signature is not required for applications with a student PI.

Department or Division Chair, Center Director (or counterpart) of PI: (or Vice-Chair or Chair's designee if Chair is investigator or otherwise unable to review): I certify that this research is appropriate for this Principal Investigator, that the investigators are qualified to conduct the research, and that there are adequate resources (including financial, support and facilities) available. If my unit has a local review committee for pre-IRB review, this requirement has been satisfied. I support this application, and hereby submit it for further review.

_____ _____

Signature of Department Chair or designee Date

_____ _____

Print Name of Department Chair or designee Department

Part A.2. Summary Checklist *Are the following involved?*

	Yes	No
A.2.1. Existing data, research records, patient records, and/or human biological specimens?	__	_X_
A.2.2. Surveys, questionnaires, interviews, or focus groups with subjects?	X__	__
A.2.3. Videotaping, audiotaping, filming of subjects, or analysis of existing tapes?	__	_X_
A.2.4. Do you have specific plans to enroll subjects from these vulnerable or select populations:		
a. UNC-CH students or UNC-CH employees?	_X_	__
b. Non-English-speaking?	__	_X_
c. Decisionally impaired?	__	_X_
d. Patients?	_X_	__
e. Prisoners, others involuntarily detained or incarcerated, or parolees?	__	_X_
f. Pregnant women?	__	_X_
g. Minors (less than 18 years)? ***If yes***, give age range: to years	__	_X_
A.2.5. a. Are sites outside UNC-CH engaged in the research?	__	_X_
b. Is UNC-CH the sponsor or lead coordinating center for a multi-site study?	__	_X_
If yes, include the ***Addendum for Multi-site Studies***.		
If yes, will any of these sites be outside the United States?	__	__
If yes, is there a local ethics review committee agency with jurisdiction? (provide contact information)	__	__
A.2.6. Will this study use a data and safety monitoring board or committee?	__	_X_
If yes: UNC-CH School of Medicine DSMB? (must apply separately)	__	__
Lineberger Cancer Center DSMC?	__	__
Other? Specify:	__	__
A.2.7. a. Are you collecting sensitive information such as sexual behavior, HIV status, recreational drug use, illegal behaviors, child/physical abuse, immigration status, etc?	__	_X_
b. Do you plan to obtain a federal Certificate of Confidentiality for this study?	__	_X_
c. Is this research classified (e.g., requires security clearance)?	__	_X_
A.2.8. a. Investigational drugs? (provide **IND #**)	__	_X_
b. Approved drugs for "non-FDA-approved" conditions?	__	_X_
All studies testing substances in humans must provide a letter of acknowledgement from the UNC Health Care Investigational Drug Service (IDS).		
A.2.9. Placebo(s)?	__	__X
A.2.10. Investigational devices, instruments, machines, software? (provide **IDE #**)	__	_X_
A.2.11. Fetal tissue?	__	_X_
A.2.12. Genetic studies on subjects' specimens?	_X_	__
A.2.13. Storage of subjects' specimens for future research? ***If yes, see instructions for Consent for Stored Samples.***	_X_	__
A.2.14. Diagnostic or therapeutic ionizing radiation, or radioactive isotopes, which subjects would not receive otherwise? ***If yes, approval by the UNC-CH Radiation Safety Committee is required.***	__	__ X
A.2.15. Recombinant DNA or gene transfer to human subjects? ***If yes, approval by the UNC-CH Institutional Biosafety Committee is required.***	__	_X_
A.2.16. Does this study involve UNC-CH cancer patients? ***If yes, submit this application directly to the Oncology Protocol Review Committee.***	__	_X_
A.2.17. Will subjects be studied in the Clinical and Translational Research Center (CTRC) or is the CTRC involved in any other way with this study? If yes, obtain the ***CTRC Addendum*** *and submit completed application (IRB application and Addendum) directly to the CTRC. The CTRC includes facilities located on the 3rd floor of the Main Hospital (formerly GCRC) and Ground floor Burnett-Womack (formerly CCCT).*	__	_X_
A.2.18. Will gadolinium be administered as a contrast agent?	__	__X
A.2.19. Will subjects' Social Security Number (SSN) be collected for:		
a. processing payments greater than $200 per year, to support IRS reporting (see also B.6)?	__	_X_
b. processing payments of any amount through UNC-CH Accounts Payable?	__	_X_
c. use as a unique identifier for study tracking purposes for national registry or database?	__	_X_

Part A.3. Conflict of Interest Questions and Certification

The following questions apply to **all investigators and study staff** engaged in the design, conduct, or reporting results of this project **and/or their immediate family members.** For these purposes, "family" includes the individual's spouse and dependent children. "Spouse" includes a person with whom one lives together in the same residence and with whom one shares responsibility for each other's welfare and shares financial obligations.

A.3.1. Currently or during the term of this research study, does any member of the research team or his/her family member have or expect to have:		
(a) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with the sponsor of this study?	__ yes	_X_ no
(b) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with an entity that owns or has the right to commercialize a product, process or technology studied in this project?	__ yes	_X_ no
(c) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with an entity engaged in the performance of this project as a subcontractor, sub-recipient or vendor?	__ yes	_X_ no
(d) A board membership of any kind or an executive position (paid or unpaid) with the sponsor of this study or with an entity that owns or has the right to commercialize a product, process or technology studied in this project?	__ yes	_X_ no
A.3.2. Has the University or has a University-related foundation received a cash or in-kind gift from the sponsor of this study for the use or benefit of any member of the research team?	__ yes	_X_ no
A.3.3. Has the University or has a University-related foundation received a cash or in-kind gift for the use or benefit of any member of the research team from an entity that owns or has the right to commercialize a product, process or technology studied in this project?	__ yes	_X_ no

If the answer to ANY of the questions above is *yes*, the affected research team member(s) must complete and submit the form, which is accessible online at http://coi.unc.edu. List name(s) of all research team members for whom any answer to the questions above is *yes*:

_____

Certification by Principal Investigator: By submitting this IRB application, I (the PI) certify that the information provided above is true and accurate regarding my own circumstances, that I have inquired of every UNC-Chapel Hill employee or trainee who will be engaged in the design, conduct or reporting of results of this project as to the questions set out above, and that I have instructed any such person who has answered "yes" to any of these questions to complete and submit for approval a Conflict of Interest Evaluation Form. I understand that as Principal Investigator I am obligated to ensure that any potential conflicts of interest that exist in relation to my study are reported as required by University policy.

_____ _____

Signature of Principal Investigator Date

Faculty Advisor if PI is a Student or Trainee Investigator: I accept ultimate responsibility for ensuring that the PI complies with the University's conflict of interest policies and procedures.

_____ _____

Signature of Faculty Advisor Date

Signature of Faculty Advisor Date

Part A.4. Questions Common to All Studies

For all questions, if the study involves only secondary data analysis, focus on your proposed design, methods and procedures, and not those of the original study that produced the data you plan to use.

Complete answers must be provided. While you may reference other documents with supporting information, do not respond solely by stating "see attached."

A.4.1. **Brief Summary**. Provide a *brief* non-technical description of the study, which will be used in IRB documentation as a description of the study. Typical summaries are 50-100 words. *Please reply to each item below, retaining the subheading labels already in place, so that reviewers can readily identify the content.*

Purpose: The purpose of this protocol is to compare the genetic and epigenetic effects between diesel exhaust and ozone exposure in healthy individuals and in mild/moderate asthmatics.

Participants: We will recruit up to 30 mild to moderate asthmatics and up to 50 healthy adults to participate in this study.

Procedures (methods): Subjects will be exposed to clean air, to 300 $\mu g/m^3$ of diesel exhaust for 2 hours and to 0.3 ppm of ozone for 2 hours with intermittent exercise in a controlled environment chamber. Primary endpoints will include spirometry and lung cell changes post-exposure. Secondary endpoints will include analysis of blood clotting/coagulation factors, Holter monitoring of cardiac parameters, analysis of soluble factors present in plasma and bronchial lavage and analysis of intracellular factors present in lung tissue obtained from a brush biopsy.

A.4.2. **Purpose and Rationale**. Provide a summary of the background information, state the research question(s), and tell why the study is needed. If a complete rationale and literature review are in an accompanying grant application or other type of proposal, only provide a brief summary here. If there is no proposal, provide a more extensive rationale and literature review, including references.

Several epidemiological studies have shown a strong link between exposure to air pollution and adverse cardiopulmonary effects, such as respiratory tract infections, exacerbation of asthma, chronic bronchitis, ischemic heart disease, and stroke(Brunekreef and Holgate 2002; Riedl and Diaz-Sanchez 2005; Lewtas 2007). Ozone and diesel exhaust are ubiquitous in the urban atmosphere making it difficult to identify the exact source of these effects. Although experimental chamber studies have been previously performed with diesel exhaust or ozone, no one has yet looked at the epigenetic changes resultant from acute exposures to these air pollutants.

Numerous studies have shown that healthy subjects exposed to ozone have decreased pulmonary function and increased neutrophils and soluble pro-inflammatory mediators in the lower airways(Peden, Setzer et al. 1995; Bascom 1996). These include markers of increased permeability, decreased macrophage phagocytic ability, and increases in arachidonic acid metabolites, cytokines, fibronectin, lactase dehydrogenase, coagulation factor VII, tissue factor, elastase and plasminogen activator occurred in response to ozone-induced exposures(Devlin, McDonnell et al. 1991; Koren, Devlin et al. 1991; McDonnell, Kehrl et al. 1991; Devlin 1993; McKinnon, Madden et al. 1993). Diesel exhaust fumes contain primarily fine and ultrafine carbonaceous particles generated by the incomplete combustion of fuel(Diaz-Sanchez, Penichet-Garcia et al. 2000; Lewtas 2007). Diesel exhaust particles (DEP) are the largest single source of vehicular emitted airborne PM and can persist in the air, where they are readily inhaled and deposited throughout the respiratory tract. DEP induced toxicity is mainly attributed to its chemical composition, consisting of a carbonaceous core to which organic and inorganic species can become adsorbed (Brunekreef and Holgate 2002; Riedl and Diaz-Sanchez 2005). Healthy human volunteers exposed to 300 $\mu g/m^3$ diesel exhaust for one hour with intermittent exercise resulted in markers of systemic and redox-sensitive pulmonary inflammatory responses, vascular dysfunction and impaired endogenous fibrinolysis. Although there were no adverse health effects associated with the exposure, acute changes in the aforementioned endpoints can be used to extrapolate information in order to begin to understand the underlying biological mechanisms that link long-

term exposure of diesel exhaust inhalation to the pathogenesis of atherothrombosis and acute myocardial infarction (Salvi, Blomberg et al. 1999; Behndig, Mudway et al. 2006).

Previous studies reported a wide variation in response to air pollution exposure among individuals in each subject group with no clear understanding in reasons (McDonnell 1991). Asthmatics have been identified as a susceptible subpopulation as seen by their heightened sensitivity to air pollutants, although the severity of health responses of asthmatics exposed to diesel exhaust and ozone are not yet fully understood. It is hypothesized that increased susceptibility could be due to increased baseline airway inflammation and airway responsiveness which characterizes asthma. Indeed, respirable particulate matter and ozone exposure are associated with episodes of increased asthma exacerbation (Devlin 1993; Bascom 1996; Diaz-Sanchez and Riedl 2005). Elevated levels of air pollution can affect airway reactivity with decrements in several indices of pulmonary function especially in those patients with preexisting asthma.

Despite a decade of intensive studies, adverse health effects attributed to air pollutant exposure are still not well understood. It is becoming increasingly clear that epigenetics plays a pivotal role in disease development and outcome, which has been extensively studied in cancer. The term epigenetics refers to the study of heritable gene expression changes, which occur without changing the DNA sequence itself. DNA methylation, histone modifications and microRNA expression all regulate gene expression, and changes in these mechanisms can result in an overall change in gene expression patterns. Unlike the static DNA sequence, these mechanisms are regulated by endogenous and exogenous cues, rendering them more likely to change in response to environmental stimuli. It is not currently known how these changes become permanent, or how epigenetic changes control gene expression in response to acute environmental perturbations. Few studies have examined how the environment can modulate epigenetic marks in individuals. In a pioneering study published in 2005, Fraga et. al. showed that as identical twins age, DNA methylation patters change indicating that differential gene expression observed in older identical twins may be attributed to epigenetic changes, further suggesting that these changes may have been molded by the environment (Fraga, Ballestar et al. 2005). Traffic particle exposure has been associated with methylation changes in retrotransposable elements, randomly dispersed throughout the DNA sequence, however the biological consequence of this is not understood as these are not coding sequences (Baccarelli, Wright et al. 2009). In vitro studies in primary human bronchial epithelial cells grown at air liquid interface showed that microRNA expression profiles change rapidly in response to exposure to diesel exhaust particles(Jardim 2009). Animal studies attempting to address these questions have been difficult as animals have very different epigenetic mechanisms making it difficult to draw conclusions from these studies. Long term exposure to cigarette smoke, a source of particulates, lead to changes in microRNA expression in rat lungs, however the contribution of these changes to biological consequences is not currently known (Izzotti, Calin et al. 2009). Another study, showed that an in utero diet rich in methyl donors enhanced allergic airway disease in mice via changes in methylation of several genes, and that these changes were transgenerational (Hollingsworth, Maruoka et al. 2008). While it is difficult to draw biological meaning from epigenetic animal studies, what these studies show is that the environment can play an important role in regulating gene expression. Although the biological and physiological role epigenetics plays in response to environmental pollutants is not yet understood, however we will begin to address this question in this study by performing in depth gene expression analysis, including microarrays, microRNA arrays and DNA methylation assays on samples collected from patients.

In addition to possible epigenetic mechanisms, genetic polymorphisms, particularly polymorphisms in anti-oxidant genes, have been proposed as a factor to explain variability in these responses. The role of genetic background in mediating airway and vascular inflammation following acute exposure to diesel exhaust and ozone in human subjects will be studied in this protocol as a secondary question. As such, bronchial epithelial cells collected from this study will be further evaluated by in vitro exposure to both gaseous and particulate air pollution.

The purpose of this study is to first, make a direct comparison of epigenetic responses (primarily changes in DNA methylation, microRNA expression and chromatin modification) in individuals exposed to ozone and diesel exhaust; second, to assess whether mild to moderate asthmatics exhibit the similar effects and to the same degree as healthy individuals; and third, to understand the contribution of genetic background and epigenetic mechanisms to cardiopulmonary effects observed in pollutant exposed cells. Although many the observed adverse health effects are generally attributed to oxidative stress upon exposure, we still do not know how these result in physiological changes to the respiratory and cardiovascular organ systems. We hypothesize that exposure to diesel exhaust or ozone will result in changes in epigenetic mechanisms, which may be linked to adverse health effects of exposure. If adverse health effects are induced solely due to oxidative stress, then patients should exhibit similar cardiopulmonary and epigenetic responses when exposed to either, diesel exhaust or ozone. However, if differential

responses to these agents are observed, then alternative mechanisms of cellular injury may exist. Therefore, we will employ several methods to assess potentially important physiological changes to these systems, including cutting edge techniques such as micro-array profiling, DNA methylation assays, microRNA expression profiling and assays for indications of chromatin remodeling.

Baccarelli, A., R. O. Wright, et al. (2009). "Rapid DNA methylation changes after exposure to traffic particles." Am J Respir Crit Care Med **179**(7): 572-8.

Bascom, R. (1996). "Environmental factors and respiratory hypersensitivity: the Americas." Toxicol Lett **86**(2-3): 115-30.

Behndig, A. F., I. S. Mudway, et al. (2006). "Airway antioxidant and inflammatory responses to diesel exhaust exposure in healthy humans." Eur Respir J **27**(2): 359-65.

Brunekreef, B. and S. T. Holgate (2002). "Air pollution and health." Lancet **360**(9341): 1233-42.

Devlin, R. B. (1993). "Identification of subpopulations that are sensitive to ozone exposure: use of end points currently available and potential use of laboratory-based end points under development." Environ Health Perspect **101 Suppl 4**: 225-30.

Devlin, R. B., W. F. McDonnell, et al. (1991). "Exposure of humans to ambient levels of ozone for 6.6 hours causes cellular and biochemical changes in the lung." Am J Respir Cell Mol Biol **4**(1): 72-81.

Diaz-Sanchez, D., M. Penichet-Garcia, et al. (2000). "Diesel exhaust particles directly induce activated mast cells to degranulate and increase histamine levels and symptom severity." J Allergy Clin Immunol **106**(6): 1140-6.

Diaz-Sanchez, D. and M. Riedl (2005). "Diesel effects on human health: a question of stress?" Am J Physiol Lung Cell Mol Physiol **289**(5): L722-3.

Folinsbee, L. J., J. F. Bedi, et al. (1985). "Pulmonary response to threshold levels of sulfur dioxide (1.0 ppm) and ozone (0.3 ppm)." J Appl Physiol **58**(6): 1783-7.

Fraga, M. F., E. Ballestar, et al. (2005). "Epigenetic differences arise during the lifetime of monozygotic twins." Proc Natl Acad Sci U S A **102**(30): 10604-9.

Hollingsworth, J. W., S. Maruoka, et al. (2008). "In utero supplementation with methyl donors enhances allergic airway disease in mice." J Clin Invest **118**(10): 3462-9.

Izzotti, A., G. A. Calin, et al. (2009). "Downregulation of microRNA expression in the lungs of rats exposed to cigarette smoke." FASEB J **23**(3): 806-12.

Jardim, M., Fry, RC, Jaspers, I, Dailey, L and Diaz-Sanchez, D (2009). "Disruption of MicroRNA Expression in Human Airway Cells by Diesel Exhaust Particles is Linked to Tumorgigenesis-Associated Pathways." Environmental Health Perspectives **117**(11).

Koren, H. S., R. B. Devlin, et al. (1991). "Time-dependent changes of markers associated with inflammation in the lungs of humans exposed to ambient levels of ozone." Toxicol Pathol **19**(4 Pt 1): 406-11.

Lewtas, J. (2007). "Air pollution combustion emissions: characterization of causative agents and mechanisms associated with cancer, reproductive, and cardiovascular effects." Mutat Res **636**(1-3): 95-133.

McDonnell, W. F. (1991). "Intersubject variability in human acute ozone responsiveness." Pharmacogenetics **1**(2): 110-3.

McDonnell, W. F., H. R. Kehrl, et al. (1991). "Respiratory response of humans exposed to low levels of ozone for 6.6 hours." Arch Environ Health **46**(3): 145-50.

McKinnon, K. P., M. C. Madden, et al. (1993). "In vitro ozone exposure increases release of arachidonic acid products from a human bronchial epithelial cell line." Toxicol Appl Pharmacol **118**(2): 215-23.

Peden, D. B., R. W. Setzer, Jr., et al. (1995). "Ozone exposure has both a priming effect on allergen-induced responses and an intrinsic inflammatory action in the nasal airways of perennially allergic asthmatics." Am J Respir Crit Care Med **151**(5): 1336-45.

Riedl, M. and D. Diaz-Sanchez (2005). "Biology of diesel exhaust effects on respiratory function." J Allergy Clin Immunol **115**(2): 221-8; quiz 229.

Salvi, S., A. Blomberg, et al. (1999). "Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers." Am J Respir Crit Care Med **159**(3): 702-9.

A.4.3. **Subjects.** *You should describe the subject population even if your study does not involve direct interaction (e.g., existing records).* Specify number, gender, ethnicity, race, and age. Specify whether subjects are healthy volunteers or patients. If patients, specify any relevant disease or condition and indicate how potential subjects will be identified. Researchers are reminded that additional approvals

may be needed from relevant "gatekeepers" to access subjects (e.g., school principals, facility directors, hospital or healthcare system administrators).

Subjects for this study will be healthy adults, 18-55 years old, (male and female) and, otherwise healthy, 18-55 year old mild to moderate asthmatics (as defined by NHLBI guidelines), who are non-smoking. Subjects will be recruited through the Westat Corporation (see section B1 below). There are no gender or race based restrictions. Pregnant and lactating women will be excluded because of the unknown effects of air pollutants on inflammatory markers during pregnancy and lactation.

A.4.4. **Inclusion/exclusion criteria.** List required characteristics of potential subjects, and those that preclude enrollment or involvement of subjects or their data. Justify exclusion of any group, especially by criteria based on gender, ethnicity, race, or age. If pregnant women are excluded, or if women who become pregnant are withdrawn, specific justification must be provided.

Healthy Individuals

Specific Inclusion Criteria

1. Physical exams will be performed by study physicians during the screening visit (IRB approved EPA protocol 95-EPA-66).
2. Normal lung function (pre or post albuterol), defined by Knudson 1976/1984 as:
   a. FVC of $\geq$ 75 % of that predicted for gender, ethnicity, age and height.
   b. FEV_1 of $\geq$ 75 % of that predicted for gender, ethnicity, age and height.
   c. FEV_1/FVC ratio of $\geq$ 75 % of predicted values.
3. Oxygen saturation of $\geq$ 96 %.
4. Ability to tolerate intervals of moderate exercise

Exclusion Criteria:

1. A history of chronic illnesses such as diabetes, rheumatological diseases, immunodeficiency state, known clinically significant cardiac disease (including myocardial infarction, congestive heart failure and angina), chronic respiratory diseases such as chronic obstructive pulmonary disease, and lung cancer.
2. If the subject is pregnant, attempting to become pregnant or breastfeeding.
3. Allergy to any medications which may be used or prescribed in the course of this study.
4. Subjects currently taking mega doses of vitamins and supplements, homeopathic/naturopathic medicines or medications which may impact the results of the PM and/or ozone challenge or interfere with any other medications potentially used in the study (to include systemic steroids and beta blockers). Subjects must refrain from all over the counter anti-inflammatory agents including those for allergies, and naproxen, and anti-oxidants for a period of one week prior to exposure. Medications not specifically mentioned here may be reviewed by the investigators prior to a subject's inclusion in the study.
5. Smoking history within 2 years of the study.
6. Use of inhaled steroids, cromolyn, or leukotriene inhibitors (Montelukast, Zafirkulast, etc) initiated within the past month (except for use of cromolyn exclusively prior to exercise). Patients must be on a stable regimen of therapy.
7. Untreated hypertension (> 150 systolic, > 90 diastolic)
8. Dementia.
9. Unspecified illnesses, which in the judgment of the investigator might increase the risk associated with PM inhalation challenge or exercise, will be a basis for exclusion.
10. History of skin allergy to tape or electrodes.
11. Subjects who do not understand or speak English
12. Subjects who are unable to perform moderate exercise

Temporary exclusions:

1. Viral upper respiratory tract infection or any acute infection requiring antibiotics within 6 weeks of bronchoscopy.
2. Use of daily medications(at the discretion of physician)
3. Symptom score greater than 20 (out of a possible 60-see accompanying score sheet) for total symptom score with a value greater than 3 for any one score. Only one score may be equal to 3.
4. Current exacerbation of allergic rhinitis and or use of antihistamines during one week prior to exposure.
5. Recent or recurring exposure to pollutants or irritants

Exclusion criteria for bronchoscopy:

1. Any food or fluids after midnight prior to bronchoscopy
2. FEV1/FVC ratio less than 60% predicted on AM of bronchoscopy.
3. Regular use of aspirin ≥ 81 mg daily, or other nonsteroidal anti-inflammatory drugs (which inhibit platelet function).

Use of other medications will be evaluated on a case-by-case basis. There is the potential that an individual's current medication use will preclude them from participating in the study at the current time, but they may be reassessed and potentially rescheduled for participation at a later time.

Mild to Moderate Asthmatics

Inclusion Criteria:

1. Physical exams will be performed by study physicians during the screening visit (IRB approved EPA protocol 95-EPA-66) where diagnosis will be judged by EPA physicians.
2. Mild/Moderate asthmatics as defined by NHLBI guidelines.
3. Positive history of asthma (wheezing, chest tightness, and reversible airway obstruction);
4. Baseline $FEV_1/FVC \geq 60\%$;
5. Oxygen saturation of ≥ 94%
6. Ability to tolerate moderate exercise

Exclusion Criteria

1. Use of oral steroid therapy within the past month
2. Physician directed emergency treatment for asthma exacerbation within the preceding 6 months.
3. Abnormal EKG that precludes evaluating heart rate variability.
4. Aside from mild/moderate asthma, a history of chronic illnesses such as diabetes, rheumatological diseases, immunodeficiency state, known clinically significant cardiac disease (including myocardial infarction, congestive heart failure and angina), chronic respiratory diseases such as chronic obstructive pulmonary disease or severe asthma, and cancer (possible exception for history of nonmelanoma skin cancer).
5. If the subject is pregnant, attempting to become pregnant or breastfeeding.
6. Allergy to any medications which may be used or prescribed in the course of this study
7. Subjects currently taking mega doses of vitamins and supplements, homeopathic/naturopathic medicines or medications which may impact the results of the PM challenge or interfere with any other medications potentially used in the study (to include systemic steroids and beta blockers). Subjects must refrain from all over the counter anti-inflammatory agents including those for allergies, and naproxen, and anti-oxidants for a period of one week prior to exposure. Medications not specifically mentioned here may be reviewed by the investigators prior to a subject's inclusion in the study.
8. Dosing level of an inhaled steroid must be consistent with mild asthma as outlined by the NHLBI NAEPP guidelines. Regular use of oral corticosteroids, or use of inhaled steroid at doses typically used for severe asthma, will result in exclusion of that individual from the protocol.
9. Severe asthmatics as defined by: nighttime symptoms of cough or wheeze greater than 1 time per week at baseline, daily exacerbation of asthma or requirement for albuterol due to asthma symptoms (cough, wheeze, chest tightness, but not to include prophylactic use of albuterol prior to exercise), more than mild interference with normal activity, any episode of physician directed emergency treatment for asthma requiring oral corticosteroid therapy within the past twelve months.
10. Smoking history within 2 years of study.
11. Use of inhaled steroids, cromolyn, or leukotriene inhibitors (Montelukast, Zafirkulast, etc) initiated within the past month (except for use of cromolyn exclusively prior to exercise). Patients must be on a stable regimen of therapy.
12. History of skin allergy to tape or electrodes.
13. History of respiratory diseases other than allergic rhinitis and asthma
14. Untreated hypertension (> 150 systolic, > 90 diastolic)
15. Dementia.
16. Unspecified illnesses, which in the judgment of the investigator might increase the risk associated with PM inhalation challenge or exercise, will be a basis for exclusion.
17. Subjects who do not understand or speak English
18. Subjects who are unable to perform moderate exercise

Allowances: subjects may

1. Use daily theophylline therapy.
2. Use daily inhaled steroids.
3. Use inhaled cromolyn therapy.

Temporary exclusions:

1. Viral upper respiratory tract infection or any acute infection requiring antibiotics within 6 weeks of bronchoscopy.
2. Use of daily medications(at the discretion of physician)
3. Symptom score greater than 20 (out of a possible 60-see accompanying score sheet) for total symptom score with a value greater than 3 for any one score. Only one score may be equal to 3.
4. Current exacerbation of allergic rhinitis and or use of antihistamines during one week prior to exposure.
5. Recent or recurring exposure to pollutants or irritants

Exclusion criteria for bronchoscopy:

1. Any food or fluids after midnight prior to bronchoscopy
2. FEV1/FVC ratio less than 60% predicted on AM of bronchoscopy.
3. Regular use of aspirin $\geq$ 81 mg daily, or other nonsteroidal anti-inflammatory drugs (which inhibit platelet function).

Use of other medications will be evaluated on a case-by-case basis. There is the potential that an individual's current medication use will preclude them from participating in the study at the current time, but they may be reassessed and potentially rescheduled for participation at a later time.

A.4.5. **Full description of the study design, methods and procedures.** Describe the research study. Discuss the study design; study procedures; sequential description of what subjects will be asked to do; assignment of subjects to various arms of the study if applicable; doses; frequency and route of administration of medication and other medical treatment if applicable; how data are to be collected (questionnaire, interview, focus group or specific procedure such as physical examination, venipuncture, etc.). Include information on who will collect data, who will conduct procedures or measurements. Indicate the number and duration of contacts with each subject; outcome measurements; and follow-up procedures. If the study involves medical treatment, distinguish standard care procedures from those that are research. If the study is a clinical trial involving patients as subjects and use of placebo control is involved, provide justification for the use of placebo controls.

This is a randomized cross-over study with three arms. This study will compare the epigenetic responses of healthy adults and adults with mild asthma to diesel exhaust and ozone exposures. Up to fifty subjects will be recruited into the healthy adult group and up to thirty subjects into the mild to moderate asthmatic group. Subjects will be randomly exposed to clean air, diesel exhaust and ozone with exposures separated by a minimum of two weeks. Responses of primary interest will include: 1) genetic and epigenetic changes 2) FEV1 as measured by spirometry, and 3) lung inflammation and cell changes as evaluated by bronchoalveolar lavage. The performance of these tests and procedures are considered essential to conducting the study. Exploratory endpoints will include: blood CBC and differential, fibrinogen and platelets, changes in IL 6 and IL 8 comparing pre-exposure with post-exposure values. Safety endpoints will include comparison of temperature, telemetry, respiratory rate, O_2 saturation and symptoms scores for pre- and post-exposure, and at 18-24 hours post-exposure. All medical procedures will be performed by study personnel.

Up to an additional 15 healthy subjects will be recruited specifically to be exposed to ozone generated using the heavy non-radioactive isotope of oxygen (18O). There is no risk to the subject of inhaling this isotope, which is naturally occurring in small concentrations. We have previously used 18Ozone in a study approved by the UNC IRB in 1993. The purpose of these exposures is to measure the amount of 18O label attached to airway epithelial cells removed during bronchoscopy and thus calculate the dose of ozone these cells received. We will draw a small blood sample but no other tests will be performed on these subjects other than routine spirometry to ensure they are not at risk for bronchoscopy.

Physical Examination Day:

Prior to recruitment into the study, subjects will undergo a physical exam. During this visit, a short review of the subject's history will be performed and vital signs, height and weight will be assessed (temperature, pulse, respiratory rate, and blood pressure), to determine whether the individual meets any major exclusion criteria for the study. Up to 50 ml of blood may be collected for a CBC/ differential, chemistry and lipid panels, assessment of coagulation function, phagocytic function and cell surface markers. At this time the subject may undergo a physical examination for bronchoscopy or may be scheduled for one at another time.

In order to participate in this study, subjects will be asked to:

- 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.
- On the Exposure Day 2, eat a normal breakfast.
- No caffeine for 12 hours prior to all study visits.
- At the end of Exposure Day 2, do not eat or drink anything after midnight in preparation for bronchoscopy on Exposure Day 3.

Training Day

1. Eligible subjects will report to the research lab for an approximate 2-hour training session.
2. Informed consent will be obtained.
3. Assessment of **vital signs** (temperature, pulse, respiratory rate, and blood pressure), oxygen saturation
4. **Pregnancy tests** will be administered to any women who may have child-bearing potential.
5. Subjects will be trained on the cycle ergometer and the work load to elicit a minute ventilation normalized for body surface of $25L/m^2/BSA$ will be determined. In most subjects this will be about 50 L/minute (IE. VO^2 of approximately 2.0 L/m). A cycle ergometer work setting of 75 to 100 watts will usually achieve such a physiological response
6. Subjects will perform **spirometry.**
7. Subjects will be shown chamber where exposures will take place.

Exposure Day 1

The subjects will be exposed ozone, diesel exhaust and clean air on three separate occasions, with the exposures separated by a minimum of two weeks. Subjects receiving 18Ozone, will only be exposed to ozone.

1. Subjects will be asked to arrive at the study site no sooner than 8 AM and will undergo **assessment of vital signs** (temperature, pulse, respiratory rate, and blood pressure), oxygen saturation, and **symptom score** assessment.
2. **Pregnancy tests** will be administered to any women who may have child-bearing potential.
3. A **telemetry unit** will be attached for cardiac monitoring.
4. Subject will be fitted with a **Holter monitor** and the subject will be asked to recline in a quiet dark place for 30 minutes. After approximately 20 minutes a time marker will be activated so that heart rate variability frequency readings can be taken over the next 10 minutes. The subject will wear the Holter monitor for the next 24 hrs. Subjects exposed to 18Ozone will not be fitted with a Holter.
5. **Venipuncture:** Up to 80 ml of blood will be collected for a CBC/ differential, and may be used for assessment of coagulation function and markers, phagocytic function, inflammation, and cell surface markers. A portion of the sample may be used for RNA isolation for microarray analysis and for DNA isolation for genotyping purposes. Pre-exposure blood will not be taken from subjects being exposed to 18Ozone
6. **Baseline Spirometry**
7. **Exposure sessions**: Exposure to ozone, diesel exhaust or clean air will be conducted in an exposure chamber at the EPA Human Studies Facility on the UNC campus. Each subject will be exposed up to 0.3ppm ozone, diesel exhaust (up to 300 ug/m^3) or clean air for 2 hours. Subjects will begin exercising on an exercise bike. Each exercise session will consist of a 15 minute exercise interval at a level of up to 25 L/m2/BSA followed by a 15 minute rest period. Minute ventilation may be measured during each exercise period. Continuous heart rate and rhythm, and oxygen saturation, will be monitored using telemetry and pulse oximetry respectively. Blood pressure may be monitored intermittently. Subjects will be asked to refrain but not prohibited from using inhaled bronchodilator during exposures; if medication use is necessary subjects will be instructed to maintain consistent medication use across the two exposures. The subjects will be able to end their exposure and exit the chamber at any time. Indications for terminating the

exposure include significant respiratory distress or dyspnea, chest or angina-like pain, significant cardiac arrhythmias, pallor, ataxia, or a greater than 5 point drop in saturated oxygen (or a drop to lower than 89%). They will be monitored continuously by trained personnel and a physician is on call whenever a subject is undergoing a procedure at the facility. A detailed description of the physical facilities in the Human Studies Division of the U.S. EPA Health Effects Research Laboratory located on the UNC-CH campus have been published as U.S. Government Publication EPA-600/1-78-064, and is on file in the office of the UNC Committee on the Protection of the Rights of Human Subjects. The medical station of the Human Studies Division includes a fully-equipped medical examination room, a cardiac/respiratory emergency cart, a subject recovery room, a nurse's station, a waiting room and conference rooms. The facility is staffed by qualified RNs, and an on-site physician is available to respond to a medical emergency in a timely manner. The exposure atmosphere will be at approximately 40 $\pm$ 10% RH and approximately 22 $\pm$ 2 °C. The DE will be generated from a diesel generator used to power a load bank that is located outside the Human Studies Facility, and subsequently introduced into the exposure chamber after different dilutions with clean HEPA and charcoal filtered and humidified air to give a chamber concentration of up to 300 $\mu g/m^3$. The monitoring analyzer registers a concentration in real time. Exposures will be terminated at values $\geq$ 400 $\mu g/m^3$ during runs in which the exposure targets 300 $\mu g/m^3$ DE. This safety limit will prevent an inhalational exposure greater than 1080 µg, which assumes that the subject will inhale 2.7 m^3 during the 120 min exposure. Levels of carbon monoxide (CO), and oxides of nitrogen (NOx; mainly NO, and some NO_2), will be kept under 10 ppm CO, 15 ppm NO, and 2.5 ppm NO_2 or the exposure will be terminated. [The OSHA 8 hr time-weighted average (TWA) for these substances are: CO=50 ppm; NO=25 ppm; NO_2=5 ppm; Diesel fuel used for the study will be purchased as a commercial ultra low sulfur fuel. Subjects will enter the exposure chamber (about 6 ft x 6 ft x 8 ft). Particle mass will be measured in real time. Particle size distribution may not be determined during each subject exposure but at regular intervals (e.g., monthly) to show that the size distribution does not change radically. Filter samples will also be analyzed for chemical composition of particles. Ozone exposures will be conducted in a (6 ft x 6 ft x 8 ft) stainless steel chamber with a continuous supply of exposure medium. Ozone will be monitored continuously. **Immediately post exposure**, subjects will again undergo **spirometry, Holter monitor frequency reading, symptom scoring and assessment of vital signs.**

8. **Then,** up to 80 ml of blood will be collected for a CBC/ differential, assessment of coagulation function, blood leukocyte phagocytic function, cytokines, cell surface markers and RNA isolation for microarray analysis. Subjects exposed to 18Ozone will have only 20 mls of blood removed for analysis of 18O tag present on blood cells and have post exposure Spirometry measurements.
9. **Subjects exposed to 18Ozone will have bronchoscopy performed about 1 hr post-exposure.** Exposure to 18Ozone and undergoing a bronchoscopy approximately one hour later should not increase the risk to the subjects. We have completed two earlier studies in which subjects underwent bronchoscopy following exposure to concentrations of ozone higher than used in this study, and encountered no problems. Others have also published studies in which subjects were exposed to ozone followed by bronchoscopy one hour later
10. Subjects will then be assessed and discharged by the nursing staff.

Exposure Day 2 (approximately 24 hours after exposure)
Subjects being exposed to 18O will not be returning for a Day 2

The subject will arrive at the U.S. EPA HSF for:

1. **Vital sign monitoring**.
2. **Symptom scoring**.
3. **Venipuncture**: up to 80 ml of blood will be collected for a CBC/ differential, coagulation function, assessment of blood monocyte phagocytic function, inflammation, and cell surface markers, and RNA isolation for microarray analysis.
4. **Holter monitor** frequency reading and removal
5. **Spirometry**
6. **Bronchoscopy.** Subjects will have undergone a physical examination including assessment for suitability for transnasal fiberoptic bronchoscopy at the Human Studies Facility by a board certified or board eligible pulmonologist.

   Prior to the procedure, subjects will perform spirometry (as above); bronchoscopy will not be performed if lung function does not meet the recommended performance level (NIH guidelines; FEV1$\geq$ 60 % predicted). Prior to bronchoscopy, a small tube (IV) will be placed in a vein for potential use in administering fluids. Subjects will receive inhaled albuterol prior to the bronchoscopy at the discretion of

the pulmonary physician performing the procedure. Bronchoscopy with bronchoalveolar lavage and brush biopsy will be performed by a licensed physician who is Board certified or board eligible in pulmonary medicine and is experienced in fiberoptic bronchoscopy. The physician will be assisted by at least one R.N experienced in bronchoscopy. The subjects will be monitored closely throughout the procedure in the following manner: 1) Chest electrodes for continuous electrocardiogram, 2) Pulse oximetry of arterial blood, and 3) blood pressure monitoring using an electronic sphygmomanometer. Subjects may be premedicated with IV atropine (0.6 mg) to prevent bradycardia and hypotension that could result from vagal stimulation provoked by passing the bronchoscope through the subject's larynx and to minimize the amount of airways secretions. Nasal oxygen will be administered during the procedure. No sedatives and/or narcotics are administered at any time during bronchoscopy. We have found that premedication with sedatives (midazolam) or with opiates (demerol) is not required for research bronchoscopy subjects. Avoidance of these drugs reduces procedure risk and markedly shortens post-procedure recovery time. Neosynephrine will be used to decongest nasal passages, followed by gargling with a lidocaine solution for a few seconds to anesthetize the throat. The subject will then sniff (snort) a small amount of lidocaine jelly through one nostril to anesthetize the nose and the back of throat. A Q-tip with lidocaine jelly will be gently inserted into the nose to ensure that it is completely numb before the bronchoscope is inserted. Topical lidocaine anesthesia will be administered to the larynx and lower airways through the bronchoscope for subject comfort and to prevent cough, with a maximum dose of 15 ml of 2% lidocaine solution (360 mg lidocaine) Up to 8 endobronchial brush biopsies will be obtained from the lower trachea and right and left mainstem bronchi. A cytology brush (Bronchoscope Cytology Brush; Bard, Tewksbury, MA) is applied to the region under direct visualization. For a single brushing, six passes, each with a linear excursion of approximately 2-5 cm, are made with the brush along the endobronchial surface. Bronchoalveolar lavage will be performed in the right middle lobe using a total volume of up to 250 cc of sterile 0.9% saline; from one to 5 aliquots of 50 cc each will be injected and immediately aspirated through the channel in the bronchoscope using a syringe.

Subjects are observed and monitored for a minimum of 1 to 2 hours after the procedure in the on-site medical station by a registered nurse with physician supervision. At discharge subjects will be symptom-free. At least 2 physicians, including the responsible bronchoscopist, will be available (24 hours daily) to subjects who develop any symptoms after discharge. The subject is discharged by a physician and is provided with the names and telephone numbers of the bronchoscopist and one other physician. The subject is contacted 24 hours post-bronchoscopy to ask about any untoward effects.

Subjects will return to the U.S. EPA HSF for an additional exposure sessions and post exposure bronchoscopies (air control, ozone or diesel exhaust) after a minimum time interval of two weeks.

We anticipate performing several clinical procedures during the course of this study which include primary, secondary and exploratory endpoints. However, it is possible that not all procedures will be performed on every subject. If we are unable to perform a procedure, because of a investigator problem (such as but not limited too building/equipment failures, weather delays, or staffing issues), then the patient will be compensated for said procedure(s) and time on that day and may be rescheduled.

A.4.6. **Benefits to subjects and/or society.** Describe any potential for direct benefit to individual subjects, as well as the benefit to society based on scientific knowledge to be gained; these should be clearly distinguished. Consider the nature, magnitude, and likelihood of any direct benefit to subjects. If there is no direct benefit to the individual subject, say so here and in the consent form (if there is a consent form). Do not list monetary payment or other compensation as a benefit.

There will be no direct benefit to the subject for participating, other than information that may be learned during their physical examination about their overall physical status. The primary benefit from the study will be to add to the scientific knowledge about whether exposure to air pollutants induces epigenetic changes.

A.4.7. **Full description of risks and measures to minimize risks.** Include risk of psychosocial harm (e.g., emotional distress, embarrassment, breach of confidentiality), economic harm (e.g., loss of employment or insurability, loss of professional standing or reputation, loss of standing within the

community) and legal jeopardy (e.g., disclosure of illegal activity or negligence), as well as known side effects of study medication, if applicable, and risk of pain and physical injury. Describe what will be done to minimize these risks. Describe procedures for follow-up, when necessary, such as when subjects are found to be in need of medical or psychological referral. If there is no direct interaction with subjects, and risk is limited to breach of confidentiality (e.g., for existing data), state this.

Risk and Procedures for Minimizing Risks of Diesel Exhaust Exposure

- Diesel Exhaust Exposure: The amount of diesel exhaust used for exposure in this study would be equivalent to concentrations of diesel exhaust particulate matter that would be encountered at busy intersections in large urban area. These concentrations are the occupational levels for some truck drivers (generally about 100-300 $\mu g/m^3$) and 1-2 mg/m^3 for some mines. Some areas of heavily trafficked streets in Los Angeles and New York City have had diesel exhaust levels >20 $\mu g/m^3$, and nearby residents could have exposure to these concentrations over several hours. Controlled diesel exhaust exposure studies in Sweden using 300 $\mu g/m^3$ DEP have shown lung inflammatory effects not unlike effects observed with numerous ozone exposure studies performed here at the EPA facility on the UNC campus during the past 20 yr. Diesel exhaust particles contain some probable carcinogenic polycyclic aromatic hydrocarbons, which in high enough concentrations and/or with repeated exposures may induce tumors. Diesel exhaust also contains aldehydes, some of which are possibly carcinogenic in high enough dose and with long enough exposure. However, the exposure concentrations to be used in this protocol are minimal. Overall, it appears that at the low DEP concentration to be given one time for the exposure in this study, the risk of cancer, if it exists at all, is extremely low and certainly no more than what one would experience if one were to visit for a few days a particulate-polluted city in the US such as Los Angeles or New York City. We have seen in IRB-07-0190 that exposure to 300 $\mu g/m^3$of diesel exhaust does not cause adverse health effects.

Health effects of acute exposures to air pollution particles are not well defined but possibly include chest pain, mild dyspnea, headache, cough, and, in some subjects, wheezing. All of these effects resolve spontaneously within hours of exposure cessation. In the pilot phase of study #07-0190 (Haiyan Tong MD, Ph.D, PI), subjects reported "moderate" eye irritation following diesel exhaust exposure and the symptom was resolved within a few hours after the exposure. Subjects will be provided with the choice to wear chemical safety goggles during exposures to prevent or minimize the eye irritation. During exposure, subjects will be monitored by direct observation or via closed-circuit television. Subjects will have EKG leads attached during the exposure to monitor cardiac function during exercise. Subjects will be aware that they can terminate their exposure for any reason and still receive compensation for their participation up to that point. The investigators or duty physician will end the exposure if the subject is found to be suffering from any significant adverse effect. No major adverse health effects were observed in a recently completed study that exposed subjects (18-35 yr old, healthy volunteers) to concentrated Chapel Hill air particles here at the EPA facility (Physiological and Biochemical Changes Associated with Exposure to Air Pollution Particles; Andrew Ghio, MD, PI; UNC IRB# 95-EPA-310). The maximum PM concentration reached 311 $\mu g/m^3$ during the exposure. The data from this exposure study suggest that normal healthy subjects tolerate inhalation of concentrated ambient PM fairly well, and support the idea that exposures to lower PM concentrations, including DEP, will be fairly safe in terms of cardiopulmonary responses. For safety reasons, pulse oximetry will be performed during the exposures to diesel exhaust and filtered air, and the subject withdrawn from the chamber if the O_2 saturation value is <89%. Additionally subjects will have carboxyhemoglobin values determined within 1 hr after an exposure and kept at the Medical Station if levels are >20% (where performance of everyday cognitive tasks may be jeopardized) until levels become <20%; but because the CO levels are expected to be 2-4 ppm [based on preliminary chamber characterizations], levels are expected to be < 5%.

A duty physician is always onsite to respond to an emergency. Fully equipped resuscitation equipment is available for use in the event of a cardiac or pulmonary emergency. Physicians at the University of North Carolina (UNC) Hospitals Emergency Room are also available to assist in treatment of an emergency.

Heart rate, electrocardiogram, and pulse oximetry will be monitored continuously. Subjects will also be monitored for significant respiratory distress or dyspnea, chest pain, significant cardiac arrhythmias, pallor, and ataxia. Subjects will be aware that they can terminate their exposure for any reason and still receive compensation for the entire exposure session. The investigator or duty physician will end the exposure if the subject is found to be suffering from any adverse effect.

Risk and Procedures for Minimizing Risks of Ozone Exposure

Potential risks may likely include mild airway obstruction, irritation to the nose, eyes, throat and airways, pain on deep inspiration and cough. These symptoms typically disappear 2 to 4 hours after exposure, but may last longer for

particularly sensitive people. Ozone may induce an inflammatory reaction that may last for about 24-48 hours after exposure and may increase the chance of catching a cold. It is likely that most subjects participating in this study will experience some degree of tracheobronchial irritation and cough. There is no additional risk associated with the heavy isotope (18O) of ozone.

Risks and Procedures for Minimizing Risks of Venipuncture:

Insertion of the needle may cause minor discomfort at the site of injection and there is a possibility that a bruise will form which may be painful for 2-3 days. It is possible that the subject may feel lightheaded or even faint due to anxiety about the blood draw. Rarely, a skin infection may occur. To minimize these risks, blood is drawn by trained medical professionals. Subjects are closely monitored for any signs of faintness, given liquids and food to eat if requested, and only allowed to leave the facility after a 15-minute waiting period to make sure they are stable.

Risks and Procedures for Minimizing Risks of Bronchoscopy:

The most significant risk to a volunteer in this protocol involves bronchoscopy. Over 1000 procedures have been performed within the EPA Human Studies Facility over the past 15 years. From January 1, 1986 through December 30, 1995, 736 procedures were performed in normal nonasthmatic subjects, and these have been reported in the Journal of Bronchology 1998; 5:185-194. The overall complication rate was less than 1% (actually less than 0.1%). The most frequent complication was a low grade fever. Bronchoscopy with BAL can be associated with more significant complications, including hypoxemia, cough, wheezing, and post-bronchoscopy fever. These may be increased in asthmatic subjects, and some investigators have found hypoxemia to be more severe in asthmatics compared to normal subjects (Djukanović, R., J. W. Wilson, C. K. Lai, S. T. Holgate, and P. H. Howarth. 1991. The safety aspects of fiberoptic bronchoscopy, bronchoalveolar lavage, and endobronchial biopsy in asthma. *Am. Rev. Respir. Dis.* 143: 772-777), while others have not (Van Vyve, T., P. Chanez, J. Bousquet, J. Y. Lacoste, F. B. Michel, and P. Godard. 1992. Safety of bronchoalveolar lavage and bronchial biopsies in patients with asthma of variable severity. *Am. Rev. Respir. Dis.* 146: 116-121); Anonymous. Workshop summary and guidelines: investigative use of bronchoscopy, lavage, and bronchial biopsies in asthma and other airway disease. *J Allergy Clin Immunol* 88:808-14, 1991.;
Jarjour NN, Peters SP, Djukanovic R, Calhoun WJ. Investigative use of bronchoscopy in asthma. Am J Respir Crit Care Med 157:692-97, 1998.) Furthermore, hypoxemia is rarely severe enough to require premature termination of the procedure and can usually be treated or prevented by supplemental oxygen (Van Wyre).

Bronchoscopies are performed by experienced physicians who are either Board-certified or Board-eligible in pulmonary medicine. The physician performing the bronchoscopy is always assisted by at least one nurse familiar with the procedure. The subject's vital signs and ECG are continuously monitored during the bronchoscopic procedures and at regular intervals during the recovery phase. The procedure is immediately terminated if the subject experiences any alterations such as tachypnea, depressed respiration, tachycardia, bradycardia, abnormal rhythms or significant changes in blood pressure. As indicated earlier, a fully equipped emergency cart including a defibrillator, endotracheal intubation equipment and emergency medications (atropine, epinephrine) is available at all times. An on-site physician is always available to respond and the UNC Memorial Hospital Emergency Room is within 1/4 mile of Human Studies Facility. Before the subject is sent home, he/she receives a brief physical examination by a physician and is given phone numbers and a pager number with which to contact a physician should he/she experience any problems or have any questions.

The complication rate during medical bronchoscopy is approximately 0.08 to 0.12% for all events, including low oxygen saturation, respiratory embarrassment, myocardial infarction, or death. The medical screening of the subjects is specifically designed to exclude subjects with a history of medical problems which might put them at risk from the particle exposure and bronchoscopic procedures. Medical problems which could arise as a result of bronchoalveolar lavage and brush biopsy include the following:

Discomfort of the nose and throat is a primary risk of bronchoscopy. As outlined, the lidocaine gargle, spray and liquid is used to anesthetize these areas prior to passing the bronchoscope to reach the lower airways. The procedure will be discontinued if adequate anesthesia cannot be achieved by the means described.

Low-grade fever (38-38.5 °C) can occur in approximately 25 % of hospitalized subjects undergoing bronchoscopy. The fever invariably resolves within 18 hours without treatment or with acetaminophen. Our experience at HSD, EPA has shown that this fever and the associated malaise can almost always be prevented by administering ibuprofen following the procedure. The subject will be asked to contact the physician who performed the procedure or one of the nurses at the Medical Station if fever persists or is higher than 38.5 °C. As part of the standard protocol, a nurse or physician will contact the subject by telephone between 24 and 48 hours after the procedure to inquire on the general health of the subject and specifically about the presence of fever.

Cough is a common, albeit minor, problem encountered during bronchoscopy. Cough results from mechanical stimulation of cough receptors in the airway by the bronchoscope or the cytologic brush used for the brush biopsies. In addition to the discomfort, prolonged coughing with the bronchoscope in place can result in mild mechanical

trauma to the vocal cords. Lidocaine solution is passed through the bronchoscope channel at the main carina and at the level of the right mainstream bronchus to suppress the cough reflex during the procedure, more can be used as needed. The procedure will be terminated if adequate cough suppression cannot be attained.

Epistaxis is caused by trauma to the nose by the bronchoscope. This condition is expected to be minor and resolve on its own. Small streaks of blood in nasal secretions may be present for up to 12 hours following the procedure. If the bleeding becomes moderate or severe during bronchoscopy, the procedure will be terminated and the bronchoscope removed. The subject's anterior nasal passage will be packed with sterile gauze to stop the bleeding. If the bleeding does not resolve with packing, the subject will be transferred to the UNC Hospital Emergency Room.

Lidocaine use presents a small risk to the subjects, as a variable fraction of the medication is absorbed through the airway mucosa. If a significant amount of lidocaine is absorbed, adverse reactions such as bradycardia, hypotension, urticarial reactions, confusion, lightheadedness, euphoria, tremors and seizures can result. We take particular precautions to avoid the possibility of overdose of topical lidocaine and limit the total amount of lidocaine instilled into the airways to a maximum of 360 mg. Also, subjects will be screened by history prior to the procedure for known allergies to lidocaine or other similar topical anesthetics.

Bronchospasm, manifested as wheezing, chest tightness or dyspnea, is a risk of bronchoscopy that is caused by stimulation of irritant receptors in the airways by the bronchoscope. This risk is minimized by 1) only allowing persons with stable mild to moderate stable asthma to participate in the study, 2) pretreatment with inhaled bronchodilator before the procedure per request of the bronchoscopy physician 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 physicians responsible for the procedure. Administration of inhaled bronchodilator (albuterol) is all that should be required to control the symptoms. In the unlikely event that the subject requires additional treatment because the asthma attack continues, they will be transported by ambulance to the emergency room of the UNC Hospital Emergency Room.

Pneumothorax is a risk of bronchoscopic procedures such as transbronchial biopsy, peripheral lung protected brushings or peripheral lung cytology brushings. Because these procedures will not be performed, the risk of pneumothorax in this study is extremely small. There is a very small risk of a pneumothorax resulting from a endobronchial brush biopsy. The symptoms include dyspnea and chest pain. The subjects will be interviewed and examined by the bronchoscopy physician 2 hours after the procedure with these symptoms in mind. If a pneumothorax is suspected, the subject will be transferred to the UNC Hospital Emergency Room by ambulance for further evaluation and treatment.

Bleeding in the lower airway may occur from trauma caused by the bronchoscope or by brush biopsy. Bleeding is typically very minor, in the order of 1/10 cc, is not clinically significant in an otherwise healthy subject and should spontaneously resolve in a matter of minutes. Epinephrine, diluted 1/20,000 fold will be administered through the bronchoscope to the affected site if bleeding is minor to moderate. The maximum dose of epinephrine used will be 2-3 cc to prevent local tissue necrosis. The site will be monitored through the bronchoscope until the bleeding stops. If bleeding fails to resolve with epinephrine or if it is sufficiently severe to cause hemoptysis or hemoglobin desaturation, oxygen supplementation will be provided to keep arterial oxygen saturation above 90% and the subject will be transported to the NC Memorial Hospital Emergency Room by ambulance. If it becomes necessary, the subject can be intubated before transport.

The use of epinephrine to control bleeding can produce systemic effects resulting from mucosal absorption of the drug. These symptoms are transient and include headache, palpitations and tachycardia when the dose is greater than 1 mg and is given intravenously. Two cc of a 1/20, 000 dilution of epinephrine contains 0.10 mg of the drug, a dose that is very unlikely to induce any untoward effects. This is especially true when the drug is applied to the mucosa, since only a fraction is expected to be absorbed.

Bradycardia and/or hypotension may result from increased vagal nerve output provoked by coughing or Valsalva during the passage of the bronchoscope through the vocal cords and trachea. Atropine (0.6 mg iv) is prophylactically administered to the subjects before the start of the procedure to minimize this risk. The primary side effects associated with atropine administration is mild sinus tachycardia which typically resolves within 30 minutes as the drug is cleared from the subject's system. In rare cases (less than 1 percent) the sinus tachycardia is accompanied by hypotension.

Hypoxemia: Arterial blood oxygen saturation is continuously monitored during the procedure with a finger pulse oximeter. Subjects are supplemented with oxygen at a flow rate of 2 l/min via nasal cannula during the procedure. The oxygen flow can be increased to a maximum of 6 l/min if the arterial oxygen saturation falls below 93 %. If oxygen supplementation is not effective, the procedure will be discontinued immediately. Removal of the bronchoscope and treatment with inhaled bronchodilator should be sufficient to allow the subject's arterial oxygen saturation to return to normal. Under normal conditions, oxygen supplementation is ceased once the procedure is completed. However, supplementation will be continued if arterial oxygen saturation is below 93 % on room air. In the event that low oxygen saturation persists, if the subject cannot be weaned from the oxygen supplementation, or if it falls precipitously at any time, an emergency situation will be declared and the subject will be transported immediately by ambulance to the UNC Hospital Emergency Room. These risks are minimized during the research

procedure at the Human Studies Facility, in part because premedication with sedatives (midazolam) or with opiates (demerol) (as is used in medical bronchosopy) is not required for healthy research subjects. Avoiding these drugs reduces procedure risk and allows the participants to enjoy a normal day after leaving the EPA Human Studies Facility.

The risk of pneumonia as a result of bronchoalveolar lavage in the lobe involved in the procedure is less than 1%. Symptoms of pneumonia could include fever, dyspnea, persistent cough, productive cough and chest pain. The subject will be instructed to call the physician who performed the procedure or the Medical Station if these symptoms occur. The medical staff will evaluate the subject over the phone between 24 and 48 hours after the procedure for signs of pneumonia.

The subject will be urged to contact the Medical Station or the bronchoscopy physician should he/she experience any of the following symptoms: 1) Epistaxis, 2) Persistent cough, 3) Hemoptysis, 4) Chest pain, 5) Dyspnea, 6) Wheezing, 7) Sputum production, 8) Hoarseness or sore throat.

Confidentiality Risk

Risk of breach of confidentiality is minimal. For the mild asthmatic subject, it is conceivable that an employer or insurance company could learn of the diagnosis if the subject requires medical intervention as a result of participating in the study. All subjects will be assigned a study number which will be used for data recording – not the subject's name. The study number is all that will be entered into computer databases. All paper files which may contain the subject's name or screening number are secure in the EPA building which has limited access 24 hours/day. Any abnormal medical findings (CBC, ECG, spirometry) will be discussed with the subject and the subject will be counseled to seek treatment from his/her personal physician if indicated. Samples will be stored at the U.S. EPA HSF. A numeric coding system will be used to ensure that subjects cannot be directly identified from the samples alone.

A.4.8. **Data monitoring and analysis.** Tell how the qualitative and/or quantitative data will be analyzed. Explain how the sample size is sufficient to achieve the study aims. This might include a formal power calculation or explanation of why a small sample is sufficient (e.g., qualitative research, pilot studies). Describe the provisions for monitoring the data to ensure the safety of participants. These plans could range from the investigator monitoring subject data for any safety concerns to a sponsor-based DSMB, depending on the study.

The research objective of this study is to determine if changes in epigenetic mechanisms in bronchial epithelial cells can be linked to physiological changes in healthy and mild/moderate asthmatic volunteers safely exposed to low levels of O3 and diesel exhaust. The study will follow a randomized, repeated measures design with each subject exposed to clean air, diesel exhaust and ozone. The data analysis will be focused on changes in lung function measurements, primarily FVC and FEV_1, and secondarily, HRV measurements between pre and post 2hr exposure for each exposure and lung cell composition changes. Also blood endpoints include inflammatory factors (eg IL-6), blood clotting factors (eg fibrinogen), and susceptibility factors (eg specific genotypes associated with susceptibility to air pollution).

In evaluating exposure effects of O3 and DE upon lung function, the difference between the pre-exposure and post-exposure FEV1 will be calculated and the pre-post differences for the air and the exposures will be compared utilizing repeated measures ANOVA parametric test. Clinically significant change is determined to be a 10% decrease in FEV1 measured prior to and immediately after the exposure compared to the pre exposure value. For a conservative sample size calculation, we used one sided test for a single sample under the assumption of normal distribution with Type I error of 5% and Type II error of 20%. Therefore, a ρ value of 0.05 or less will be considered significant and the proposed sample size will provide adequate (80%) power for detecting a 10% decrease in ΔFEV1.

Sample size calculation was based on the Forced Expiratory Volume in 1 Second (FEV1) in response to the O3 exposure. Data for the power calculation were obtained from results of FEV_1 (Folinsbee, Bedi et al. 1985) for a constant acute exposure to 0.3 ppm O_3 versus filtered air. In 22 subjects, the pre exposure FEV_1 was 4.608 ± 0.514 (mean $\pm$ SEM) in FA exposure and 4.656 ± 0.592 in O_3. The post exposure FEV_1 was 4.64 ± 0.476 in FA exposure and 3.856 ± 0.687 in O_3. We used 0.687 as an estimate of standard deviation after the ozone exposure and estimated 10% decrease in pre-exposure FEV1 levels to be 0.46 ml. Based on these data the required sample size for each

group is 30 subjects. We will initially recruit 30 subjects for each group (healthy and mild/moderate asthmatics) for this study to ensure the statistical power that can analyze small differences expected from low concentration exposures.

Other Exploratory Observations:
We hypothesize that subjects harboring polymorphisms in antioxidant genes will have increased responses to diesel exhaust and ozone compared to subjects who do not. In order to address this we will use collected cell samples for in vitro exposure experiments

Exploratory endpoints will include the effect of diesel exhaust and ozone on changes in: blood CBC and differential, fibrinogen and platelets, changes in IL 6 and IL 8 comparing pre-exposure with post-exposure values.

A.4.9. **Will you collect or receive any of the following identifiers?** Does not apply to consent forms.

__ No _X_ Yes *If yes, check all that apply*:

a. _X_ Names
b. _X_ Telephone numbers
c. _X_ Any elements of dates (other than year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death. For ages over 89: all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 and older
d. _X_ Any geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code
e. __ Fax numbers
f. _X_ Electronic mail addresses
g. __ Social security numbers
h. _X_ Medical record numbers
i. __ Health plan beneficiary numbers
j. __ Account numbers
k. __ Certificate/license numbers
l. __ Vehicle identifiers and serial numbers (VIN), including license plate numbers
m. __ Device identifiers and serial numbers (e.g., implanted medical device)
n. __ Web universal resource locators (URLs)
o. __ Internet protocol (IP) address numbers
p. __ Biometric identifiers, including finger and voice prints
q. __ Full face photographic images and any comparable images
r. __ Any other unique identifying number, code, or characteristic, other than dummy identifiers that are not derived from actual identifiers and for which the re-identification key is maintained by the health care provider and not disclosed to the researcher

A.4.10. **Identifiers in research data**. Are the identifiers in A.4.9 above linked or maintained with the research data?

_X_ yes __ no

A.4.11. **Confidentiality of the data**. Describe procedures for maintaining confidentiality of the data you will collect or will receive. Describe how you will protect the data from access by those not authorized. How will data be transmitted among research personnel? Where relevant, discuss the potential for deductive disclosure (i.e., directly identifying subjects from a combination of indirect IDs).

No personal identifying information will be attached to the samples. No subjects will be identified in any report or publication about this study. Study samples will be stored in a secure room with restricted access. The sample will be prepared and stored indefinitely in a freezer for future testing. Portions of the sample may be shared with researchers at other scientific institutions or sent to outside clinical laboratories for analysis, however, only coded samples will be sent. All medical records generated during this study will be kept in a locked file cabinet in the Medical Station at the U.S. EPA 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 a day for seven days a week

A.4.12. **Data sharing.** With whom will *identifiable* (contains any of the 18 identifiers listed in question A.4.9 above) data be shared outside the immediate research team? For each, explain confidentiality measures. Include data use agreements, if any.

_X_ No one
__ Coordinating Center:
__ Statisticians:
__ Consultants:
__ Other researchers:
__ Registries:
__ Sponsors:
__ External labs for additional testing:
__ Journals:
__ Publicly available dataset:
__ Other:

A.4.13. **Data security for storage and transmission**. Please check all that apply.

For electronic data stored on a desk top computer:
_X_ Secure network _X_ Password access __ Data encryption__ Password protected file(s)
__ Other comparable safeguard (describe):

For portable computing devices/external storage devices (e.g. laptop computer, PDA, CDs, memory sticks):
__ Power-on password __ Automatic log-off __ Data encryption __ Password protected file(s)
__ Other comparable safeguard (describe):

For hardcopy data (including human biological specimens, CDs, tapes, etc.):
__ Data de-identified by research team (stripped of the 18 identifiers listed in question A.4.9 above)
__ Locked suite or office _X_ Locked cabinet
__ Data coded by research team with a master list secured and kept separately
__ Other (describe):

A.4.14. **Post-study disposition of identifiable data or human biological materials**. Describe your plans for disposition of data or human biological specimens that are identifiable in any way (directly or via indirect codes) once the study has ended. Describe your plan to destroy identifiers, if you will do so.

Samples will be stored in a repository where only project members of the study will have access to the samples. Subjects at any time may request that their samples be no longer stored in the repository. Any analysis in progress at the time of the request or already performed prior to the request being received by the researcher will continue to be used as part of the research study. Once the researcher is notified, the subject's specimens will be destroyed.

Part A.5. The Consent Process and Consent Documentation (including Waivers)

The standard consent process is for all subjects to sign a document containing all the elements of informed consent, as specified in the federal regulations. Some or all of the elements of consent, including signatures, may be altered or waived under certain circumstances.

- If you will obtain consent in any manner, complete **section A.5.1**.
- If you are obtaining consent, but requesting a waiver of the requirement for a signed consent document, complete **section A.5.2**.
- If you are requesting a waiver of any or all of the elements of consent, complete **section A.5.3**.
- If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a *limited waiver of HIPAA authorization*. This is addressed in section B.2.

You may need to complete more than one section. For example, if you are conducting a phone survey with verbal consent, complete sections A.5.1, A.5.2, and possibly A.5.3.

A.5.1. **Describe the process of obtaining informed consent from subjects.**
Describe who will be obtaining consent (or permission) and from whom. Include discussion, as relevant, any waiting period between the initial consent discussion and obtaining consent, and steps that will be taken to minimize coercion or undue influence. If children will be enrolled as subjects, describe the provisions for obtaining parental permission and assent of the child. If decisionally impaired adults are to be enrolled, describe the provision for obtaining surrogate consent from a legally authorized representative (LAR). If non-English speaking people will be enrolled, explain how consent in the native language will be obtained. Address both written translation of the consent and the availability of oral interpretation. It is expected that the information in the consent document(s) will be communicated to participants or their LAR. *After you have completed this part A.5.1, if you are not requesting a waiver of any type, you are done with Part A.5.; proceed to Part B.*

The subject will be given an opportunity to read the consent form. At that time a member of the study team (usually the PI) will verbally describe the study and the subject will have an opportunity to ask questions or address concerns about any aspect of the study. The subject will be given a copy of the signed consent form for his/her records.

A.5.2. **Justification for a waiver of *written* (i.e., signed) consent**. *The default is for subjects to sign a written document that contains all the elements of informed consent.* Under limited circumstances, the requirement for a signed consent form may be waived by the IRB if either of the following is true. *Choose only one:*

a. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., study topic is sensitive so that public knowledge of participation could be damaging). *Participants should be asked whether they want documentation linking them with the research and the participants' wishes will govern whether they sign the form.* Note: This justification cannot be used in FDA-regulated research. __ yes __ no __ yes __ no
Explain.

b. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (e.g., phone survey).
Explain.

If you checked "yes" to either (and you are not requesting a waiver in section A.5.3) consent must be obtained orally, by delivering a fact sheet, through an online consent form, or be incorporated into the survey itself. Include a copy of the consent script, fact sheet, online consent form, or incorporated document.

→ If you have justified a waiver of written (signed) consent (A.5.2), you should complete A.5.3 *only* if your consent process will not include all the other elements of consent.

A.5.3. **Justification for a full or partial waiver of consent.** *The default is for subjects to give informed consent.* A waiver might be requested for research involving only existing data or human biological specimens (see also Part C). More rarely, it might be requested when the research design requires withholding some study details at the outset (e.g., behavioral research involving deception). In limited circumstances, parental permission may be waived. This section should also be completed for a waiver of HIPAA authorization if research involves Protected Health Information (PHI) subject to HIPAA regulation, such as patient records.

__ Requesting **waiver of some elements** (specify; see SOP 28 on the IRB web site):
__ Requesting **waiver of consent entirely**

If you check either of the boxes above, answer items a-f.. To justify a full waiver of the requirement for informed consent, you must be able to answer "yes" (or "not applicable" for question c) to items a-f. **Insert brief explanations that support your answers.**

a. Will the research involve no greater than minimal risk to subjects or to their privacy? __ yes __ no
Explain.

b. Is it true that the waiver will *not* adversely affect the rights and welfare of subjects? *(Consider the right of privacy and possible risk of breach of confidentiality in light of the information you wish to gather.)* __ yes __ no
Explain.

c. When applicable to your study, do you have plans to provide subjects with pertinent information after their participation is over? *(e.g., Will you provide details withheld during consent, or tell subjects if you found information with direct clinical relevance? This may be an uncommon scenario.)* __ yes __ not applicable
Explain.

d. Would the research be impracticable without the waiver? *(If you checked "yes," explain how the requirement to obtain consent would make the research impracticable, e.g., are most of the subjects lost to follow-up or deceased?).* __ yes __ no
Explain.

e. Is the risk to privacy reasonable in relation to benefits to be gained or the importance of the knowledge to be gained? __ yes __ no
Explain.

If you are accessing patient records for this research, you must also be able to answer "yes" to item f to justify a waiver of HIPAA authorization from the subjects.

f. Would the research be impracticable if you could not record (or use) Protected __ yes __ no

Health Information (PHI)? *(If you checked "yes," explain how* not *recording or using PHI would make the research impracticable).*
Explain.

Part B. Questions for Studies that Involve Direct Interaction with Human Subjects

→ ***If this does not apply to your study, do not submit this section.***

B.1. **Methods of recruiting.** Describe how and where subjects will be identified and recruited. Indicate who will do the recruiting, and tell how subjects will be contacted. Describe efforts to ensure equal access to participation among women and minorities. Describe how you will protect the privacy of potential subjects during recruitment. *For prospective subjects whose status (e.g., as patient or client), condition, or contact information is not publicly available (e.g., from a phone book or public web site), the initial contact should be made with legitimate knowledge of the subjects' circumstances. Ideally, the individual with such knowledge should seek prospective subjects' permission to release names to the PI for recruitment. Alternatively, the knowledgeable individual could provide information about the study, including contact information for the investigator, so that interested prospective subjects can contact the investigator.* Provide the IRB with a copy of any document or script that will be used to obtain the patients' permission for release of names or to introduce the study. Check with the IRB for further guidance.

Subjects will be recruited for this study by the Westat Corporation, which has recruited for studies at the U.S EPA HSF since 1998. The manner in which this will be done is similar that that of past U.S. EPA studies and specific recruitment procedures as per the previously UNC IRB-approved protocol, Recruitment and Screening of Potential Subjects for U.S. EPA Studies (95-EPA-66). Typical methods for recruiting may include mass mailings, fliers and print ads. Every effort will be made to recruit women and members of racial minority groups into this study. Subjects will be asked to call the recruitment office. During the telephone interview, the subjects will receive information regarding the study and their eligibility for the study will be assessed. Subjects who provide responses which indicate that they are likely to meet the criteria will be scheduled for an appointment in the Westat recruitment office in the U.S. Human Studies Facility. At that time the study protocol will be outlined, and a medical history form will be administered.

B.2. **Protected Health Information (PHI).** If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a *limited waiver of HIPAA authorization*. If this applies to your study, please provide the following information and complete Section C.

a. Under this limited waiver, you are allowed to access and use only the minimum amount of PHI necessary to review eligibility criteria and contact potential subjects. What information are you planning to collect for this purpose?

b. How will confidentiality/privacy be protected prior to ascertaining desire to participate?

c. When and how will you destroy the contact information if an individual declines participation?

B.3. **Duration of entire study and duration of an individual subject's participation, including follow-up evaluation if applicable.** Include the number of required contacts and approximate duration of each contact.

It is anticipated that the duration of this study will be approximately eighteen months. Subject recruitment and screening is expected to be continuous throughout the study until the intended number of subjects is reached.

Scheduling constraints imposed by concurrent studies in the U.S. EPA Human Studies Division are expected to limit the rate at which subjects can be exposed to 1-2 per week.

The physical examination evaluation may take up to one hour. If the subject is eligible for the study, the individual may have up to nine more visits to the research facility over approximately 6 months. A physical examination for bronchoscopy will be performed. The training day (Day 1) visit will require approximately 2 hours. Exposure day (Day 2) will last approximately 6 hours. Subjects will report to the facility at no sooner than 8 AM. The morning following the exposure, the subject will return for Day 3 which a follow-up visit which may last approximately 4 hours. Subjects will report to the facility at no sooner than 8 AM. Subjects will then return and repeat the Day 2-3 visits with the second and third exposure session. Exposure sessions will be separated by a minimum of two weeks.

B.4. **Where will the subjects be studied?** Describe locations where subjects will be studied, both on and off the UNC-CH campus.

Subjects will be seen in the U.S. EPA Human Studies Facility on Mason Farm Road in Chapel Hill.

B.5. **Privacy.** Describe procedures that will ensure privacy of the subjects in this study. Examples include the setting for interviews, phone conversations, or physical examinations; communication methods or mailed materials (e.g., mailings should not indicate disease status or focus of study on the envelope).

All interviews, phone conversations, and physical examinations will be conducted in private rooms in the U.S. EPA Human Studies Facility. This facility is guarded and only individuals working in the building have access beyond the guard's desk without an escort

B.6. **Inducements for participation.** Describe all inducements to participate, monetary or non-monetary. If monetary, specify the amount and schedule for payments and if/how this will be prorated if the subject withdraws (or is withdrawn) from the study prior to completing it. For compensation in foreign currency, provide a US$ equivalent. Provide evidence that the amount is not coercive (e.g., describe purchasing power for foreign countries). Be aware that payment over a certain amount may require the collection of the subjects' Social Security Numbers. If a subject is paid more than $200.00 per year, collection of subjects' Social Security Number is required (University policy—see SSN Guidance) using the Social Security Number collection consent addendum found under forms on the IRB website (look for Study Subject Reimbursement Form).

Subjects will receive monetary compensation for their time (approximately $12 per hour) and procedures in the study. In addition, subjects traveling from areas beyond Chapel Hill/Carrboro will be reimbursed for travel expenses commensurate with the US Government mileage rate in effect at the time. Parking will be provided or costs will be paid. Payments will be made after each segment of the study, unless the subject requests otherwise.

A subject who is unable to complete the study for voluntary reasons or failure to comply with eligibility requirements will receive full compensation for his/her participation up to that point. Subjects who are dismissed by the investigators for involuntary reasons after enrollment in the study but prior to completion will be paid for their participation up to that point

.

In the event a scheduled study activity must be cancelled by the investigators with less than 72 hours prior notice, the subject will be paid at the standard hourly rate for the time scheduled and for any procedures cancelled up to a maximum of $100. Cancellations could occur due to adverse weather conditions, equipment failure, or other unforeseen events. When feasible, the subject will be rescheduled.

The following table details the expected compensation for completion of the entire study:
Subjects will be paid approximately $12 per hour for participation in this study. If the subjects complete all three exposures with bronchoscopy, the total compensation including prestudy qualifications will be approximately $2516.

Pre-study qualifications

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

Pre-study qualification total = $50

Training Day (approximately 2 hours)

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

Training Day Total = $ 44

Subjects 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	**$1548**
TOTAL for completion of THREE exposures (including completion bonus)	**$2422**

If a subject begins but cannot complete the bronchoscopy procedure for voluntary or involuntary reasons, they will receive compensation for participation up to that point.

Subjects will be asked to bring a lunch for the exposure day and a refrigerator and microwave will be available. If a subject is terminated from the study or chooses to withdraw he/she will be reimbursed for time and procedures completed up to that time point.

B.7. **Costs to be borne by subjects.** Include child care, travel, parking, clinic fees, diagnostic and laboratory studies, drugs, devices, all professional fees, etc. If there are no costs to subjects other than their time to participate, indicate this.

There will be no cost to the subject. Subjects traveling from areas beyond Chapel Hill/Carrboro will be reimbursed for travel expenses commensurate with the U.S. Government mileage rate in effect at the time. Parking will be provided or costs will be paid. Payments will be made after each segment of the study, unless the subject requests otherwise.

Part C. Questions for Studies using Existing Data, Records or Human Biological Specimens

→ ***This section applies even if records are only used to identify potential subjects.***

→ ***If your study does not use existing data, records or specimens for any purpose, do not submit this section.***

C.1. What records, data or human biological specimens will you be using? *(check all that apply)*:

__ Data already collected for another research study
If applicant was involved in the original collection, please explain role:

__ Data already collected for administrative purposes (e.g., Medicare data, hospital discharge data)
__ Medical records (custodian may also require form, e.g., HD-974 if UNC-Health Care System)
__ Electronic information from clinical database (custodian may also require form)
__ Patient specimens (tissues, blood, serum, surgical discards, etc.)
__ Other (specify):

C.2. For each of the boxes checked in 1, how were the original data, records, or human biological specimens collected? Describe the process of data collection including consent, if applicable.

C.3. For each of the boxes checked in 1, where do these data, records or human biological specimens currently reside?

C.4. For each of the boxes checked in 1, do you have permission from the custodians of the data, records or human biological specimens (e.g., pathology dept, tissue bank, original researcher)? Include data use agreements, if required by the custodian of data that are not publicly available.

C.5. If the research involves human biological specimens, has the purpose for which they were collected been met before removal of any excess? For example, has the pathologist in charge or the clinical laboratory director certified that the original clinical purpose has been satisfied? Explain if necessary.

__ yes __ no __ not applicable (explain)

C.6. Do *all* of these data, records or specimens exist at the time of this application? If not, explain how prospective data collection will occur.

__ yes __ no If no, explain

SUBJ #_____ DATE_____

SYMPTOM QUESTIONNAIRE FOR CHAMBER EXPOSURE STUDIES

Pre-Exposure / End Exposure / 24 hrs post end Exposure (Circle one)

INSTRUCTIONS: Please indicate if you are experiencing any of the symptoms or restrictions listed below, using the following scale to indicate the severity. Circle the number.

0 = NONE (not present)
1 = TRACE/NOTICED (barely detectable)
2 = MILD/LIGHT (present, but not annoying)
3 = MODERATE (present, but somewhat annoying)
4 = SEVERE/HEAVY (present and very annoying and painful)

SYMPTOMS	NONE	TRACE	MILD	MODERATE	SEVERE
1. HEADACHE	0	1	2	3	4
2. IRRITATION OF THE NOSE	0	1	2	3	4
3. STUFFY NOSE/SINUS CONGESTION	0	1	2	3	4
4. RUNNY NOSE	0	1	2	3	4
5. DRY/SORE THROAT	0	1	2	3	4
6. PAIN on DEEP INSPIRATION	0	1	2	3	4
7. UNUSUAL FATIGUE OR TIREDNESS	0	1	2	3	4
8. EYE IRRITATION	0	1	2	3	4
9. SHORTNESS OF BREATH	0	1	2	3	4
10. SNEEZING	0	1	2	3	4
11. COUGH	0	1	2	3	4
12. WHEEZING/WHISTLING in CHEST	0	1	2	3	4
13. CHEST TIGHTNESS	0	1	2	3	4
14. SWEATING	0	1	2	3	4
15. Other_____	0	1	2	3	4

IRB Notice
IRB
to:
David Diaz-Sanchez
07/13/2011 11:52 AM
Cc:
Mike Schmitt, Kelly Duncan, Kelly Duncan, Howard Kehrl
Show Details

To: David Diaz Sanchez
Environmental Protection Agency
7315

From: Biomedical IRB

Approval Date: 7/12/2011
Expiration Date of Approval: 9/19/2011

RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)
Submission Type: Modification
Expedited Category: Minor Change to Previously Approved Research
Study #: 09-1625
Study Title: Epigenetic Effects of Diesel Exhaust and Ozone Exposure
Sponsors: US Environmental Protection Agency - GRANTS

This submission has been approved by the above IRB for the period indicated. It has been determined that the risk involved in this modification is no more than minimal. Unless otherwise noted, regulatory and other findings made previously for this study continue to be applicable.

Submission Description:
This amendment received 7/6/11 addresses clarification of last modification that subjects who have previously participated may be contacted and invited to enroll in this arm.

Investigator's Responsibilities:
Enclosed are stamped copies of approved consent documents and other recruitment materials (when applicable). You must copy the stamped consent forms for use with subjects unless you have approval to do otherwise.
This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40 CFR 26 (EPA), where applicable.

CC: Michaekl Schmitt, Environmental Protection Agency; Kelly Duncan, Enviro Med Asthma And Lung Bio; Duncan Kelly; Howard Kehrl, (EPA), Non-IRB Review Contact

IRB Informational Message—please do not use email REPLY to this address

THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
Medical School Building 52
Mason Farm Road
CB #7097
Chapel Hill, NC 27599-7097
(919) 966-3113
Web site: ohre.unc.edu
https://my.research.unc.edu for IRB status
Federalwide Assurance (FWA) #4801

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Environmental Protection Agency
7315

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Investigator's Responsibilities:
Enclosed are stamped copies of approved consent documents and other recruitment materials (when applicable). You must copy the stamped consent forms for use with subjects unless you have approval to do otherwise.
This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40 CFR 26 (EPA), where applicable.

CC: Michaekl Schmitt, Environmental Protection Agency; Kelly Duncan, Enviro Med Asthma And Lung Bio; Duncan Kelly; Howard Kehrl, (EPA), Non-IRB Review Contact

THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
Medical School Building 52
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CB #7097
Chapel Hill, NC 27599-7097
(919) 966-3113
Web site: ohre.unc.edu
https://my.research.unc.edu for IRB status
Federalwide Assurance (FWA) #4801

To: David Diaz Sanchez
Environmental Protection Agency
7315

From: Biomedical IRB

Approval Date: 8/22/2011
Expiration Date of Approval: 8/20/2012

RE: Notice of IRB Approval by Full Board Review
Submission Type: Renewal
Study #: 09-1625
Study Title: Epigenetic Effects of Diesel Exhaust and Ozone Exposure
Sponsors: US Environmental Protection Agency - GRANTS

This submission has been approved by the above IRB for the period indicated.

Study Description:
Purpose: The purpose of this protocol is to compare the genetic and epigenetic effects between diesel exhaust and ozone exposure in healthy individuals and in mid/moderate asthmatics. Participants: The PI will recruit up to 30 mild to moderate asthmatics and up to 30 healthy adults to participate in this study. Procedures (methods): Subjects will be exposed to clean air, to 300 ug/m3 of diesel exhaust for 2 hours and to 0.3 ppm of ozone for 2 hours with intermittent exercise in a controlled environment chamber. Primary endpoints will include spirometry and lung cell changes post-exposure. Secondary, endpoints will include analysis of soluble factors present in plasma and bronchial lavage and analysis of intracellular factors present in lung tissue obtained from a brush biopsy.

Regulatory and other findings:
Based on the information provided, the IRB has determined that HIPAA does not apply to this study.

Social security numbers (SSN) may be collected for this study for tax identification purposes. The subject is required to disclose his/her SSN in order to receive the incentive payment(s).

Investigator's Responsibilities:
Federal regulations require that all research be reviewed at least annually. It is the Principal Investigator's responsibility to submit for renewal and obtain approval before the expiration date. You may not continue any research activity beyond the expiration date without IRB approval. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.

Enclosed are stamped copies of approved consent documents and other recruitment materials (when applicable). You must copy the stamped consent forms for use with subjects unless you have

THIS CONSENT DOCUMENT SHOULD BE USED ONLY
BETWEEN 8-22-11 AND 8-20-12
APPROVED BY
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: August 4th, 2011

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

Principal Investigator: David Diaz-Sanchez, Ph.D. and Kelly Duncan, Ph.D.
Department: United States Environmental Protection Agency
Phone number: 919-966-0676

Study Coordinator: Michael T. Schmitt, MSPH
Phone: 919-966-0647
Schmitt.mike@epa.gov

Other Contact Information: Kelly Duncan, Ph.D.
Phone: 919-966-5445
Duncan.kelly@epa.gov

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 clean air 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 With 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.

Are there any reasons you should not participate?

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 7 visits to the research facility over approximately 3-4 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 minute ventilation normalized for body surface of 25L/min/m^2BSA 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 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 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

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 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 cannulawill 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 may repeat the spirometry lung function test if the physician deems it necessary. 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 mg 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 sign the section under ***Subject's Agreement to Participate in the Research Study Without Genotyping Consent*** 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. With your permission, we will continue to store any samples that we collect and possibly use them for other studies. You will be given a separate consent form for this storage but you do not have to allow your samples to be stored indefinitely in order to participate in this study. 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, and 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 air pollution. 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. However, if possible, we may chose to use a different chamber, one which is as large as a full size living room and has a separate (private) bathroom inside.

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** those 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 is 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 that 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 complete both exposure sessions of this study, your total compensation including screening will be approximately $1742

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

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***.

- -

IRB Study: # 09-1625

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

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

Subject's Agreement to Participate in the Research Study *with* Genotyping Consent:

I have read the information provided above. I voluntarily **AGREE** to participate in this study and I voluntarily **AGREE** 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

- -

IRB Study: # 09-1625

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

Principal Investigator: 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	

THIS CONSENT DOCUMENT SHOULD BE USED ONLY
BETWEEN 8-22-11 AND 8-2012
APPROVED BY
INSTITUTIONAL REVIEW BOARD, UNC-CHAPEL HILL

University of North Carolina at Chapel Hill
Consent for Storing Biological Specimens With Identifying Information

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IRB Study # 09-1625

Consent Form Version Date: August 4th, 2011

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

Principal Investigator: David Diaz-Sanchez, Ph.D. and Kelly Duncan, Ph.D.
UNC-Chapel Hill Department: US EPA
UNC-Chapel Hill Phone number: 919-966-0676
Email Address: Diaz-Sanchez.David@epa.gc

Co-Investigators: Kelly Duncan, Ph.D. and Mike Schmitt, MSPH
Funding Source and/or Sponsor: EPA funds

Study Coordinator: Mike Schmitt, MSPH
Study Contact telephone number: 919-966-0647
Study Contact email: Schmitt.mike@epa.gov

What are some general things you should know about research?
Research is designed to gain scientific information that may help other people in the future. You may not receive any direct benefit from participating. There also may be risks. You may refuse to take part in research.

Details are discussed below. It is important that you understand this information so that you can make an informed choice. You will be given a copy of this consent form. You should ask the researchers 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 specimen repository or "biobank?"
Research with blood, tissue or body fluids (specimens) can help researchers understand how the human body works. Research can also answer other questions by using specimens. Researchers may develop new tests to find diseases, or new ways to treat diseases. In the future, research may help to develop new products, such as drugs. Specimens are commonly used for genetic research. Sometimes researchers collect and store many specimens together and use them for different kinds of research, or share them with other scientists; this is called a specimen repository or "biobank."

The purpose of this particular repository or biobank is to:

- 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.
- Store samples of respiratory cells and blood samples. These collections are part of the protocol described in the accompanying consent form **Consent to Participate in a Research Study** and the components stored represent excess tissues that are not immediately required for the study but may have value for future research.
- Cells from the lung 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.
- Research reports have suggested that people with particular genes are more susceptible to air pollutants. The epithelial specimens will be genotyped for those specific genes related to adverse health effects of air pollutant exposure.
- Studies of gene expression represent one type of genetic research. thus future investigations involving these specimens are intrinsically of a genetic nature.

All samples will be stored where only project members will have access to the samples. There is a need to store samples in such a repository because this will be an ongoing study where samples from subjects will be collected over an extended period of time. Storing of samples allows for all samples to be processed at the same time and also allows our scientist the opportunity to further study these samples with as yet unknown questions and techniques.

How will the specimens be collected?

Samples will be collected in the following manner.

- Lung cell collection. Cells will be collected from the airways and airspaces of the lung by bronchoscopy with bronchoalveolar lavage and brush biopsy. (This procedure is explained in separate consent.) Fluid will be collected into specimen tubes and placed on ice. The cells will be separated from the fluid by centrifugation (very fast spinning whereby the cells will separate from the liquid and fall to the bottom of the tube), and both samples may be processed immediately, or frozen for later analysis.
- Blood collection. You will have up to 80 cc (about 5 tablespoons) of blood per sample collected from an arm vein by our trained nursing staff. The blood will be placed into specially designed blood collection tubes which allow separation of the fluid and cell portions of blood. Those samples may be processed immediately, or be frozen for later analysis.

What will happen to the specimens?

Samples will be stored at the U.S. Environmental Protection Agency Human Studies Facility located in Chapel Hill, North Carolina. Only project members of the study will have access to the samples. Blood samples will be collected in order to look at but not limited to, indicators of inflammation due to the air pollution exposure. Specimens may be released to other investigators if there is a need to analyze samples with equipment that is not located at our facility.

What are the possible benefits to you?
Benefits to you are unlikely. These studies (current and future) may provide additional information that will be helpful in understanding asthma and how environmental factors affect the disease

What are the possible risks or discomforts involved with the use of your specimens?
This study might involve the following risks and/or discomforts to you:

Risk of breach of confidentiality is minimal. For the mild asthmatic subject, it is conceivable that an employer or insurance company could learn of the diagnosis if you required medical intervention as a result of participating in this study. You will be assigned a study number which will be used for data – not your name. The study number is all that will be entered into computer databases. All paper files which may contain your name or screening number are secure in the EPA building which has limited access 24 hours/day. A numeric coding system will be used to ensure that you cannot be directly identified from the samples alone.

Will there be any cost to you for storage of the specimens?
There will be no cost to you for the storage and use of the specimens for research purposes.

Will you receive anything for the use of your specimens?
You will not receive anything for taking part in this research.

Who owns the specimens?
Any blood, body fluids, or tissue specimens obtained for the purpose of this study become the exclusive property of The U.S. Environmental Protection Agency. The researchers may retain, preserve or dispose of these specimens and may use these specimens for research that may result in commercial applications. There are no plans to compensate you for any future commercial use of these specimens.

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 which 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.
Research studies may be done at many places at the same time. Your personal identifying information will not be sent to outside researchers.

No one 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, 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.

You will not be identified in any report or publication about research using your specimens. 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-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

A Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

Will researchers seek approval from you to do future studies involving the specimens?
By signing this consent form, you are giving your permission for researchers to use your specimens as described above. Current and future research is overseen by a committee called the Institutional Review Board (IRB). The role of the IRB is to protect the rights and welfare of research participants. In some cases, the IRB may require that you be re-contacted and asked for your consent to use your specimens in a specific research study. You have the right, at that future time, not to participate in any research study for which your consent is sought. Refusal to participate will not affect your medical care or result in loss of benefits to which you are entitled.

Will you receive results from research involving your specimens?
Most research with your specimens is not expected to yield new information that would be meaningful to share with you personally. There are no plans to re-contact you or other subjects with information about research results.

Can you withdraw the specimens from the research repository?
If you decide that you no longer wish for the specimens to be stored, you should contact the researchers on the front page of this form. It is best to make your request in writing.

Any analysis in progress at the time of your request or already performed prior to your request being received by the researcher will continue to be used as part of the research study. Once the researchers have been notified, your remaining specimens would be destroyed. If you do not make such a request, the specimens may be stored forever. The researchers may choose to destroy the specimens at any time.

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.

Who is sponsoring this research?

This research is funded by The U.S. Environmental Protection Agency. This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this research?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions, 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, anonymously if you wish, the Institutional Review Board at 919-966-3113 or by e-mail to IRB_ subjects@unc.edu.

Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate. I agree to my specimen(s) being stored with the identifying code(s).

_____ _____

Signature of Research Subject Date

_____

Printed Name of Research Subject

_____ _____

Signature of Research Team Member Obtaining Consent Date

_____

Printed Name of Research Team Member Obtaining Consent

THIS [illegible] USED ONLY
BETW[illegible] 5-2-11 [illegible]-12
INST[illegible] CHAPEL HILL

University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Addendum to measure the exact amount of ozone delivered to the lungs in IRB#09-1625.

Subjects 18 years of age or older
Biomedical Form

IRB Study: # 09-1625

Consent Form Version Date: August 4th. 2011

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

Principal Investigator: David Diaz-Sanchez, Ph.D. and Kelly Duncan, Ph.D.
Department: United States Environmental Protection Agency
Phone number: 919-966-0676

Study Coordinator: Michael T. Schmitt, MSPH
Phone: 919-966-0647
Schmitt.mike@epa.gov

Other Contact Information: Kelly Duncan, Ph.D.
Phone: 919-966-5445
Duncan.kelly@epa.gov

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 measure the amount of ozone that attaches to your lung cells. We will expose you to a type of ozone (18Ozone) which is not radioactive but we can detect in cells using special instruments. This 18Ozone is heavier but otherwise exactly the same as regular ozone and has the same effects, so there is no additional risk. This heavier type of ozone is naturally present in the atmosphere at low levels. We have successfully exposed volunteers to 18ozone in a previous study done in our facility in 1993. We will look for the 18Ozone in your lung cells by conducting a bronchoscopy about an hour after the exposure and also obtain a small amount of blood (about 2 tablespoons) to determine how much 18Ozone may have left the lung.

- 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 With Identifying Information.***

Are there any reasons you should not participate?

You should not participate in this study if:

- You have not already successfully completed a bronchoscopy in our facility.
- You are uncomfortable in small, enclosed spaces. The exposure chamber itself is approximately 4 x 8 x 6 feet in size.
- You are pregnant, attempting to become pregnant or nursing an infant
- You have a history of significant chronic illness.
- 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 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 week 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 ≤ 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 prior to the exposure day because of the bronchoscopy.
- 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 15 subjects in this research study.

How long will your participation last?

Your participation in this study may require up to 3 visits to the research facility over approximately 1-2 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 minute ventilation normalized for body surface of 25L/min/m^2BSA will be determined

Exposure Day: You will be asked to refrain from eating or drinking anything after midnight and should arrive at the EPA medical station no later than 8 am. You will need to wear comfortable clothes and shoes.

Prior to exposure, you will:

- Have your vital signs checked (heart rate, respiratory rate, blood pressure, oxygen saturation level). Have a pregnancy test if applicable.
- 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 monitors placed on you so that we can watch your heart rate and rhythm while you are in our facility.
- 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 to 18ozone. The amount of ozone you will be exposed to is less than what you would likely encounter over 24 hours on a smoggy day in an urban area. There is no additional risk to you during the inhalation of 18ozone. This isotope is naturally present in the atmosphere at low levels. We have successfully exposed volunteers to 18ozone in a previous study done in our facility in 1993. The exposure chamber is 4 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. We will compare the results of this breathing test with the one you performed prior

to ozone to make sure that your ability to blow out air (a measure of how well your lungs are functioning) very quickly was not decreased so much during the ozone exposure that it would be risky to perform bronchoscopy on you (exposure to ozone can affect this function in some people). We may ask you to remain in our facility for a while to see if your ability to blow out air very quickly (change in FEV1) improves (which it does in most people) and may give you some medication to reverse the effects of ozone. However, if your FEV1 remains low, we may opt to not perform the bronchoscopy on you. In this case you would be paid for the entire procedure.

- Have your vital signs checked.
- Have up to 20 mL blood drawn (about 2 tablespoons). We will test this blood to see if 18ozone was attached to any of your blood cells.
- Approximately one hour after exposure you will undergo a bronchoscopy. 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 fiber optic 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 pollutant exposure. The bronchoscope is a flexible fiber optic tube that is about two feet 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 have this procedure about an hour after your 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. 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. 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 be 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 wall of the airway several times. Up to 8 brush biopsies are taken.

Bronchoalveolar Lavage (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 cannula 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 eat 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 may repeat the spirometry lung function test if the physician deems it necessary. You will be discharged if your vital signs are stable, chest examination is normal. Prior to discharge you will be medicated with 600 mg 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. 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.

You should not participate in this study if you are unwilling or unable to remain in the local area for 24 hours following the bronchoscopy

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. With your permission, we will continue to store any samples that we collect and possibly use them for other studies. You will be given a separate consent form for this storage but you do not have to allow your samples to be stored indefinitely in order to participate in this study. 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. The ozone used in this exposure will be generated using the non-radioactive heavier version of oxygen (18O). The amount of ozone you will be exposed to is less than what you would likely encounter over 24 hours on a smoggy day in an urban area. There is no additional risk to you during the inhalation of 18ozone. It's naturally present in the atmosphere at low levels. We have successfully exposed volunteers to 18ozone in a previous study done in our facility in 1993. During ozone exposure, you may experience some minor degree of airway irritation, cough, and shortness of breath or wheezing. 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.

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 of the bronchoscopy procedure 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 be cancelled.

A second risk of bronchoscopy is **coughing** that result 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.

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 bronchoscopy 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 bronchoscopy 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 is 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. Additionally note that a death occurred in a volunteer receiving an overdose (over 1000 milligrams) of lidocaine during a bronchoscopy in a study out of 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 Environmental Public Human 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 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, however, 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 101°F) 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°F 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°F, 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.

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.

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, and will also be compensated for having blood taken as well as undergoing bronchoscopy.

1. If you complete this study, the total

   compensation excluding screening will be approximately $561

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:

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

Exposure Day (approximately 6 hours)

venipuncture (~20 ml, post)	$ 30
spirometry (before and after exposure)	$ 40
time (6 h @$12/h)	$ 72
Bronchoscopy	$350
Endobronchial Brush biopsies	$25

Total for completion of Exposure Day = $517

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 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 exposure or bronchoscopy. 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***.

IRB Study: # 09-1625

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

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

Subject's Agreement to Participate in the Research Study
I have read the information provided above. I voluntarily **AGREE** to participate in this study.

_____ _____
Signature of Research Subject Date

_____
Printed Name of Research Subject

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent

SUBJ #_____ DATE_____

SYMPTOM QUESTIONNAIRE FOR CHAMBER EXPOSURE STUDIES

Pre-Exposure / End Exposure / 24 hrs post end Exposure (Circle one)

INSTRUCTIONS: Please indicate if you are experiencing any of the symptoms or restrictions listed below, using the following scale to indicate the severity. Circle the number.

0 = NONE (not present)
1 = TRACE/NOTICED (barely detectable)
2 = MILD/LIGHT (present, but not annoying)
3 = MODERATE (present, but somewhat annoying)
4 = SEVERE/HEAVY (present and very annoying and painful)

SYMPTOMS	NONE	TRACE	MILD	MODERATE	SEVERE
1. HEADACHE	0	1	2	3	4
2. IRRITATION OF THE NOSE	0	1	2	3	4
3. STUFFY NOSE/SINUS CONGESTION	0	1	2	3	4
4. RUNNY NOSE	0	1	2	3	4
5. DRY/SORE THROAT	0	1	2	3	4
6. PAIN on DEEP INSPIRATION	0	1	2	3	4
7. UNUSUAL FATIGUE OR TIREDNESS	0	1	2	3	4
8. EYE IRRITATION	0	1	2	3	4
9. SHORTNESS OF BREATH	0	1	2	3	4
10. SNEEZING	0	1	2	3	4
11. COUGH	0	1	2	3	4
12. WHEEZING/WHISTLING in CHEST	0	1	2	3	4
13. CHEST TIGHTNESS	0	1	2	3	4
14. SWEATING	0	1	2	3	4
15. Other_____	0	1	2	3	4

APPROVED - IRB, UNC-CH
AUG 22 2011

OFFICE OF HUMAN RESEARCH ETHICS
Institutional Review Board

APPLICATION FOR IRB APPROVAL OF
HUMAN SUBJECTS RESEARCH
Version June 25, 2009

Part A.1. Contact Information, Agreements, and Signatures

Date: August 4th, 2011

IRB Study #09-1625

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

Name and degrees of Principal Investigator: David Diaz-Sanchez, Ph.D.; Kelly Duncan, Ph.D.
Department: US EPA Mailing address/CB #: 104 Mason Farm Road Chapel Hill, NC 27514

UNC-CH PID: 714339670 Pager:
Phone #: 919-966-0676 Fax #: 919-966-6271
Email Address: Diaz-Sanchez.David@epa.gov, Duncan.kelly@epa.gov

For trainee-led projects: __ undergraduate __ graduate __ postdoc __ resident __ other
Name of faculty advisor:
Department: Mailing address/CB #:

Phone #: Fax #: Email Address:

Center, institute, or department in which research is based if other than department(s) listed above:

Name of Project Manager or Study Coordinator (if any): Michael Schmitt, MSPH
Department: US EPA Mailing address/CB #: 104 Mason Farm Road Chapel Hill, NC 27514

Phone #: 919-966-0647 Fax #: 919-966-6271 Email Address: Schmitt.mike@epa.gov

List **all other project personnel** including co-investigators, and anyone else who has contact with subjects or identifiable data from subjects. **Include name, location (UNC or specific outside location), role and email address for each person who should receive electronic copies of IRB correspondence to PI.**

Robert Devlin, PhD.; Heidi Hiers, RN; Maryann Bassett, RN; Martin Case, BS; Andrew Ghio MD; Martha Sue Carraway, MD; Robert Truckner, MD;Howard Kehrl, MD; Tracey Montilla, RN; Michael Schmitt, MSPH, Sarah Snyder, B.S.; Melanie J. Jardim, Ph.D. Kristen Sanders, B.S.

Name of funding source or sponsor (*please do not abbreviate*):
__ not funded _X_ Federal __ State __ industry __ foundation __ UNC-CH
__ other (specify):

For external funding, RAMSeS proposal number (from Office of Sponsored Research): The PI is a USEPA scientist and this project is being funded by intramural EPA funds

For industry sponsored research (if applicable):

Sponsor's master protocol version #: Version date:

Investigator Brochure version #: Version date:

Any other details you need documented on IRB approval:

Checklist of Items to Include with Your Submission

Include the following items with your submission, where applicable.

- Check the relevant items below and include one copy of all checked items 1-11 in the order listed.
- Also include two additional collated sets of copies (sorted in the order listed) for items 1-7.

Applications must "stand alone" and should provide all information requested, i.e., complete answers must be contained in the application. While you may reference other documents with supporting information, do not respond solely by stating "see attached."

Applications will be returned if these instructions are not followed.

Check	Item	Total No. of Copies
□	1. This application. One copy must have original PI signatures.	3
□	2. Consent and assent forms (include DHHS-approved sample, when one exists), fact or information sheets, phone and verbal consent scripts.	3
□	3. HIPAA authorization addendum to consent form.	3
□	4. All recruitment materials including final copies of printed advertisements, audio/video taped advertisements, scripts, flyers, letters, and emails.	3
□	5. Questionnaires, focus group guides, scripts used to guide phone or in-person interviews, etc.	3
□	6. Documentation of reviews from any other committees (e.g., Clinical and Translational Research Center (CTRC), Oncology Protocol Review Committee, or local review committees in Academic Affairs).	3
□	7. Protocol, grant application or proposal supporting this submission, if any (e.g., extramural grant application to NIH or foundation, industry protocol, student proposal). This must be submitted if an external funding source or sponsor is checked on the previous page.	1
□	8. Addendum for Multi-Site Studies where UNC-CH is the Lead Coordinating Center.	1
□	9. Data use agreements (may be required for use of existing data from third parties).	1
□	10. Only for those study personnel *not* in the online UNC-CH human research ethics training database (http://cfx3.research.unc.edu/training_comp/): Documentation of required training in human research ethics.	1
□	11. For drug studies, Investigator Brochure if one exists. If none, include package insert for previously approved uses..	1

Principal Investigator: I will personally conduct or supervise this research study. I will ensure that this study is performed in compliance with all applicable laws, regulations and University policies regarding human subjects research. I will obtain IRB approval before making any changes or additions to the project. I will notify the IRB of any other changes in the information provided in this application. I will provide progress reports to the IRB at least annually, or as requested. I will report promptly to the IRB all unanticipated problems or serious adverse events involving risk to human subjects. I will follow the IRB approved consent process for all subjects. I will ensure that all collaborators, students and employees assisting in this research study are informed about these obligations. All information given in this form is accurate and complete.

_____ _____

Signature of Principal Investigator Date

Faculty Advisor if PI is a Student or Trainee Investigator: I accept ultimate responsibility for ensuring that this study complies with all the obligations listed above for the PI.

_____ _____

Signature of Faculty Advisor Date

Note: The following signature is not required for applications with a student PI.

Department or Division Chair, Center Director (or counterpart) of PI: (or Vice-Chair or Chair's designee if Chair is investigator or otherwise unable to review): I certify that this research is appropriate for this Principal Investigator, that the investigators are qualified to conduct the research, and that there are adequate resources (including financial, support and facilities) available. If my unit has a local review committee for pre-IRB review, this requirement has been satisfied. I support this application, and hereby submit it for further review.

_____ _____

Signature of Department Chair or designee Date

_____ _____

Print Name of Department Chair or designee Department

Part A.2. Summary Checklist *Are the following involved?*	Yes	No
A.2.1. Existing data, research records, patient records, and/or human biological specimens?	__	_X_
A.2.2. Surveys, questionnaires, interviews, or focus groups with subjects?	X__	__
A.2.3. Videotaping, audiotaping, filming of subjects, or analysis of existing tapes?	__	_X_
A.2.4. Do you have specific plans to enroll subjects from these vulnerable or select populations:		
a. UNC-CH students or UNC-CH employees?	_X_	__
b. Non-English-speaking?	__	_X_
c. Decisionally impaired?	__	_X_
d. Patients?	_X_	__
e. Prisoners, others involuntarily detained or incarcerated, or parolees?	__	_X_
f. Pregnant women?	__	_X_
g. Minors (less than 18 years)? ***If yes***, give age range: to years	__	_X_
A.2.5. a. Are sites outside UNC-CH engaged in the research?	__	_X_
b. Is UNC-CH the sponsor or lead coordinating center for a multi-site study?	__	_X_
If yes, include the ***Addendum for Multi-site Studies***.		
If yes, will any of these sites be outside the United States?	__	__
If yes, is there a local ethics review committee agency with jurisdiction? (provide contact information)	__	__
A.2.6. Will this study use a data and safety monitoring board or committee?	__	_X_
If yes: UNC-CH School of Medicine DSMB? (must apply separately)	__	__
Lineberger Cancer Center DSMC?	__	__
Other? Specify:	__	__
A.2.7. a. Are you collecting sensitive information such as sexual behavior, HIV status, recreational drug use, illegal behaviors, child/physical abuse, immigration status, etc?	__	_X_
b. Do you plan to obtain a federal Certificate of Confidentiality for this study?	__	_X_
c. Is this research classified (e.g., requires security clearance)?	__	_X_
A.2.8. a. Investigational drugs? (provide **IND #**)	__	_X_
b. Approved drugs for "non-FDA-approved" conditions?	__	_X_
All studies testing substances in humans must provide a letter of acknowledgement from the UNC Health Care Investigational Drug Service (IDS).		
A.2.9. Placebo(s)?	__	__X
A.2.10. Investigational devices, instruments, machines, software? (provide **IDE #**)	__	_X_
A.2.11. Fetal tissue?	__	_X_
A.2.12. Genetic studies on subjects' specimens?	_X_	__
A.2.13. Storage of subjects' specimens for future research?	_X_	__
If yes, *see instructions for* ***Consent for Stored Samples***.		
A.2.14. Diagnostic or therapeutic ionizing radiation, or radioactive isotopes, which subjects would not receive otherwise?	__	__
If yes, *approval by the* ***UNC-CH Radiation Safety*** ***Committee*** *is required.*		X
A.2.15. Recombinant DNA or gene transfer to human subjects?	__	_X_
If yes, *approval by the* ***UNC-CH Institutional Biosafety*** ***Committee*** *is required.*		
A.2.16. Does this study involve UNC-CH cancer patients?	__	_X_
If yes, *submit this application directly to the* ***Oncology Protocol Review Committee***.		
A.2.17. Will subjects be studied in the Clinical and Translational Research Center (CTRC) or is the CTRC involved in any other way with this study? If yes, obtain the ***CTRC Addendum*** *and submit completed application (IRB application and Addendum) directly to the CTRC. The CTRC includes facilities located on the 3rd floor of the Main Hospital (formerly GCRC) and Ground floor Burnett-Womack (formerly CCCT).*	__	_X_
A.2.18. Will gadolinium be administered as a contrast agent?	__	__X
A.2.19. Will subjects' Social Security Number (SSN) be collected for:		
a. processing payments greater than $200 per year, to support IRS reporting (see also B.6)?	__	_X_
b. processing payments of any amount through UNC-CH Accounts Payable?	__	_X_
c. use as a unique identifier for study tracking purposes for national registry or database?	__	_X_

Part A.3. Conflict of Interest Questions and Certification

The following questions apply to **all investigators and study staff** engaged in the design, conduct, or reporting results of this project **and/or their immediate family members.** For these purposes, "family" includes the individual's spouse and dependent children. "Spouse" includes a person with whom one lives together in the same residence and with whom one shares responsibility for each other's welfare and shares financial obligations.

A.3.1. Currently or during the term of this research study, does any member of the research team or his/her family member have or expect to have:		
(a) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with the sponsor of this study?	__ yes	_X_ no
(b) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with an entity that owns or has the right to commercialize a product, process or technology studied in this project?	__ yes	_X_ no
(c) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with an entity engaged in the performance of this project as a subcontractor, sub-recipient or vendor?	__ yes	_X_ no
(d) A board membership of any kind or an executive position (paid or unpaid) with the sponsor of this study or with an entity that owns or has the right to commercialize a product, process or technology studied in this project?	__ yes	_X_ no
A.3.2. Has the University or has a University-related foundation received a cash or in-kind gift from the sponsor of this study for the use or benefit of any member of the research team?	__ yes	_X_ no
A.3.3. Has the University or has a University-related foundation received a cash or in-kind gift for the use or benefit of any member of the research team from an entity that owns or has the right to commercialize a product, process or technology studied in this project?	__ yes	_X_ no

If the answer to ANY of the questions above is *yes*, the affected research team member(s) must complete and submit the form, which is accessible online at http://coi.unc.edu. List name(s) of all research team members for whom any answer to the questions above is *yes*:

_____

Certification by Principal Investigator: By submitting this IRB application, I (the PI) certify that the information provided above is true and accurate regarding my own circumstances, that I have inquired of every UNC-Chapel Hill employee or trainee who will be engaged in the design, conduct or reporting of results of this project as to the questions set out above, and that I have instructed any such person who has answered "yes" to any of these questions to complete and submit for approval a Conflict of Interest Evaluation Form. I understand that as Principal Investigator I am obligated to ensure that any potential conflicts of interest that exist in relation to my study are reported as required by University policy.

_____ _____

Signature of Principal Investigator Date

Faculty Advisor if PI is a Student or Trainee Investigator: I accept ultimate responsibility for ensuring that the PI complies with the University's conflict of interest policies and procedures.

_____ _____

Signature of Faculty Advisor Date

Signature of Faculty Advisor Date

Part A.4. Questions Common to All Studies

For all questions, if the study involves only secondary data analysis, focus on your proposed design, methods and procedures, and not those of the original study that produced the data you plan to use.

Complete answers must be provided. While you may reference other documents with supporting information, do not respond solely by stating "see attached."

A.4.1. **Brief Summary**. Provide a *brief* non-technical description of the study, which will be used in IRB documentation as a description of the study. Typical summaries are 50-100 words. *Please reply to each item below, retaining the subheading labels already in place, so that reviewers can readily identify the content.*

Purpose: The purpose of this protocol is to compare the genetic and epigenetic effects between diesel exhaust and ozone exposure in healthy individuals and in mild/moderate asthmatics.

Participants: We will recruit up to 30 mild to moderate asthmatics and up to 50 healthy adults to participate in this study.

Procedures (methods): Subjects will be exposed to clean air, to 300 $\mu g/m^3$ of diesel exhaust for 2 hours and to 0.3 ppm of ozone for 2 hours with intermittent exercise in a controlled environment chamber. Primary endpoints will include spirometry and lung cell changes post-exposure. Secondary endpoints will include analysis of blood clotting/coagulation factors, Holter monitoring of cardiac parameters, analysis of soluble factors present in plasma and bronchial lavage and analysis of intracellular factors present in lung tissue obtained from a brush biopsy.

A.4.2. **Purpose and Rationale**. Provide a summary of the background information, state the research question(s), and tell why the study is needed. If a complete rationale and literature review are in an accompanying grant application or other type of proposal, only provide a brief summary here. If there is no proposal, provide a more extensive rationale and literature review, including references.

Several epidemiological studies have shown a strong link between exposure to air pollution and adverse cardiopulmonary effects, such as respiratory tract infections, exacerbation of asthma, chronic bronchitis, ischemic heart disease, and stroke(Brunekreef and Holgate 2002; Riedl and Diaz-Sanchez 2005; Lewtas 2007). Ozone and diesel exhaust are ubiquitous in the urban atmosphere making it difficult to identify the exact source of these effects. Although experimental chamber studies have been previously performed with diesel exhaust or ozone, no one has yet looked at the epigenetic changes resultant from acute exposures to these air pollutants.

Numerous studies have shown that healthy subjects exposed to ozone have decreased pulmonary function and increased neutrophils and soluble pro-inflammatory mediators in the lower airways(Peden, Setzer et al. 1995; Bascom 1996). These include markers of increased permeability, decreased macrophage phagocytic ability, and increases in arachidonic acid metabolites, cytokines, fibronectin, lactase dehydrogenase, coagulation factor VII, tissue factor, elastase and plasminogen activator occurred in response to ozone-induced exposures(Devlin, McDonnell et al. 1991; Koren, Devlin et al. 1991; McDonnell, Kehrl et al. 1991; Devlin 1993; McKinnon, Madden et al. 1993). Diesel exhaust fumes contain primarily fine and ultrafine carbonaceous particles generated by the incomplete combustion of fuel(Diaz-Sanchez, Penichet-Garcia et al. 2000; Lewtas 2007). Diesel exhaust particles (DEP) are the largest single source of vehicular emitted airborne PM and can persist in the air, where they are readily inhaled and deposited throughout the respiratory tract. DEP induced toxicity is mainly attributed to its chemical composition, consisting of a carbonaceous core to which organic and inorganic species can become adsorbed (Brunekreef and Holgate 2002; Riedl and Diaz-Sanchez 2005). Healthy human volunteers exposed to 300 $\mu g/m^3$ diesel exhaust for one hour with intermittent exercise resulted in markers of systemic and redox-sensitive pulmonary inflammatory responses, vascular dysfunction and impaired endogenous fibrinolysis. Although there were no adverse health effects associated with the exposure, acute changes in the aforementioned endpoints can be used to extrapolate information in order to begin to understand the underlying biological mechanisms that link long-

term exposure of diesel exhaust inhalation to the pathogenesis of atherothrombosis and acute myocardial infarction (Salvi, Blomberg et al. 1999; Behndig, Mudway et al. 2006).

Previous studies reported a wide variation in response to air pollution exposure among individuals in each subject group with no clear understanding in reasons (McDonnell 1991). Asthmatics have been identified as a susceptible subpopulation as seen by their heightened sensitivity to air pollutants, although the severity of health responses of asthmatics exposed to diesel exhaust and ozone are not yet fully understood. It is hypothesized that increased susceptibility could be due to increased baseline airway inflammation and airway responsiveness which characterizes asthma. Indeed, respirable particulate matter and ozone exposure are associated with episodes of increased asthma exacerbation (Devlin 1993; Bascom 1996; Diaz-Sanchez and Riedl 2005). Elevated levels of air pollution can affect airway reactivity with decrements in several indices of pulmonary function especially in those patients with preexisting asthma.

Despite a decade of intensive studies, adverse health effects attributed to air pollutant exposure are still not well understood. It is becoming increasingly clear that epigenetics plays a pivotal role in disease development and outcome, which has been extensively studied in cancer. The term epigenetics refers to the study of heritable gene expression changes, which occur without changing the DNA sequence itself. DNA methylation, histone modifications and microRNA expression all regulate gene expression, and changes in these mechanisms can result in an overall change in gene expression patterns. Unlike the static DNA sequence, these mechanisms are regulated by endogenous and exogenous cues, rendering them more likely to change in response to environmental stimuli. It is not currently known how these changes become permanent, or how epigenetic changes control gene expression in response to acute environmental perturbations. Few studies have examined how the environment can modulate epigenetic marks in individuals. In a pioneering study published in 2005, Fraga et. al. showed that as identical twins age, DNA methylation patters change indicating that differential gene expression observed in older identical twins may be attributed to epigenetic changes, further suggesting that these changes may have been molded by the environment (Fraga, Ballestar et al. 2005). Traffic particle exposure has been associated with methylation changes in retrotransposable elements, randomly dispersed throughout the DNA sequence, however the biological consequence of this is not understood as these are not coding sequences (Baccarelli, Wright et al. 2009). In vitro studies in primary human bronchial epithelial cells grown at air liquid interface showed that microRNA expression profiles change rapidly in response to exposure to diesel exhaust particles(Jardim 2009). Animal studies attempting to address these questions have been difficult as animals have very different epigenetic mechanisms making it difficult to draw conclusions from these studies. Long term exposure to cigarette smoke, a source of particulates, lead to changes in microRNA expression in rat lungs, however the contribution of these changes to biological consequences is not currently known (Izzotti, Calin et al. 2009). Another study, showed that an in utero diet rich in methyl donors enhanced allergic airway disease in mice via changes in methylation of several genes, and that these changes were transgenerational (Hollingsworth, Maruoka et al. 2008). While it is difficult to draw biological meaning from epigenetic animal studies, what these studies show is that the environment can play an important role in regulating gene expression. Although the biological and physiological role epigenetics plays in response to environmental pollutants is not yet understood, however we will begin to address this question in this study by performing in depth gene expression analysis, including microarrays, microRNA arrays and DNA methylation assays on samples collected from patients.

In addition to possible epigenetic mechanisms, genetic polymorphisms, particularly polymorphisms in anti-oxidant genes, have been proposed as a factor to explain variability in these responses. The role of genetic background in mediating airway and vascular inflammation following acute exposure to diesel exhaust and ozone in human subjects will be studied in this protocol as a secondary question. As such, bronchial epithelial cells collected from this study will be further evaluated by in vitro exposure to both gaseous and particulate air pollution.

The purpose of this study is to first, make a direct comparison of epigenetic responses (primarily changes in DNA methylation, microRNA expression and chromatin modification) in individuals exposed to ozone and diesel exhaust; second, to assess whether mild to moderate asthmatics exhibit the similar effects and to the same degree as healthy individuals; and third, to understand the contribution of genetic background and epigenetic mechanisms to cardiopulmonary effects observed in pollutant exposed cells. Although many the observed adverse health effects are generally attributed to oxidative stress upon exposure, we still do not know how these result in physiological changes to the respiratory and cardiovascular organ systems. We hypothesize that exposure to diesel exhaust or ozone will result in changes in epigenetic mechanisms, which may be linked to adverse health effects of exposure. If adverse health effects are induced solely due to oxidative stress, then patients should exhibit similar cardiopulmonary and epigenetic responses when exposed to either, diesel exhaust or ozone. However, if differential

responses to these agents are observed, then alternative mechanisms of cellular injury may exist. Therefore, we will employ several methods to assess potentially important physiological changes to these systems, including cutting edge techniques such as micro-array profiling, DNA methylation assays, microRNA expression profiling and assays for indications of chromatin remodeling.

Baccarelli, A., R. O. Wright, et al. (2009). "Rapid DNA methylation changes after exposure to traffic particles." Am J Respir Crit Care Med **179**(7): 572-8.

Bascom, R. (1996). "Environmental factors and respiratory hypersensitivity: the Americas." Toxicol Lett **86**(2-3): 115-30.

Behndig, A. F., I. S. Mudway, et al. (2006). "Airway antioxidant and inflammatory responses to diesel exhaust exposure in healthy humans." Eur Respir J **27**(2): 359-65.

Brunekreef, B. and S. T. Holgate (2002). "Air pollution and health." Lancet **360**(9341): 1233-42.

Devlin, R. B. (1993). "Identification of subpopulations that are sensitive to ozone exposure: use of end points currently available and potential use of laboratory-based end points under development." Environ Health Perspect **101 Suppl 4**: 225-30.

Devlin, R. B., W. F. McDonnell, et al. (1991). "Exposure of humans to ambient levels of ozone for 6.6 hours causes cellular and biochemical changes in the lung." Am J Respir Cell Mol Biol **4**(1): 72-81.

Diaz-Sanchez, D., M. Penichet-Garcia, et al. (2000). "Diesel exhaust particles directly induce activated mast cells to degranulate and increase histamine levels and symptom severity." J Allergy Clin Immunol **106**(6): 1140-6.

Diaz-Sanchez, D. and M. Riedl (2005). "Diesel effects on human health: a question of stress?" Am J Physiol Lung Cell Mol Physiol **289**(5): L722-3.

Folinsbee, L. J., J. F. Bedi, et al. (1985). "Pulmonary response to threshold levels of sulfur dioxide (1.0 ppm) and ozone (0.3 ppm)." J Appl Physiol **58**(6): 1783-7.

Fraga, M. F., E. Ballestar, et al. (2005). "Epigenetic differences arise during the lifetime of monozygotic twins." Proc Natl Acad Sci U S A **102**(30): 10604-9.

Hollingsworth, J. W., S. Maruoka, et al. (2008). "In utero supplementation with methyl donors enhances allergic airway disease in mice." J Clin Invest **118**(10): 3462-9.

Izzotti, A., G. A. Calin, et al. (2009). "Downregulation of microRNA expression in the lungs of rats exposed to cigarette smoke." FASEB J **23**(3): 806-12.

Jardim, M., Fry, RC, Jaspers, I, Dailey, L and Diaz-Sanchez, D (2009). "Disruption of MicroRNA Expression in Human Airway Cells by Diesel Exhaust Particles is Linked to Tumorgigenesis-Associated Pathways." Environmental Health Perspectives **117**(11).

Koren, H. S., R. B. Devlin, et al. (1991). "Time-dependent changes of markers associated with inflammation in the lungs of humans exposed to ambient levels of ozone." Toxicol Pathol **19**(4 Pt 1): 406-11.

Lewtas, J. (2007). "Air pollution combustion emissions: characterization of causative agents and mechanisms associated with cancer, reproductive, and cardiovascular effects." Mutat Res **636**(1-3): 95-133.

McDonnell, W. F. (1991). "Intersubject variability in human acute ozone responsiveness." Pharmacogenetics **1**(2): 110-3.

McDonnell, W. F., H. R. Kehrl, et al. (1991). "Respiratory response of humans exposed to low levels of ozone for 6.6 hours." Arch Environ Health **46**(3): 145-50.

McKinnon, K. P., M. C. Madden, et al. (1993). "In vitro ozone exposure increases release of arachidonic acid products from a human bronchial epithelial cell line." Toxicol Appl Pharmacol **118**(2): 215-23.

Peden, D. B., R. W. Setzer, Jr., et al. (1995). "Ozone exposure has both a priming effect on allergen-induced responses and an intrinsic inflammatory action in the nasal airways of perennially allergic asthmatics." Am J Respir Crit Care Med **151**(5): 1336-45.

Riedl, M. and D. Diaz-Sanchez (2005). "Biology of diesel exhaust effects on respiratory function." J Allergy Clin Immunol **115**(2): 221-8; quiz 229.

Salvi, S., A. Blomberg, et al. (1999). "Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers." Am J Respir Crit Care Med **159**(3): 702-9.

A.4.3. **Subjects.** *You should describe the subject population even if your study does not involve direct interaction (e.g., existing records).* Specify number, gender, ethnicity, race, and age. Specify whether subjects are healthy volunteers or patients. If patients, specify any relevant disease or condition and indicate how potential subjects will be identified. Researchers are reminded that additional approvals may be needed from relevant "gatekeepers" to access subjects (e.g., school principals, facility directors, hospital or healthcare system administrators).

Subjects for this study will be healthy adults, 18-55 years old, (male and female) and, otherwise healthy, 18-55 year old mild to moderate asthmatics (as defined by NHLBI guidelines), who are non-smoking. Subjects will be recruited through the Westat Corporation (see section B1 below). There are no gender or race based restrictions. Pregnant and lactating women will be excluded because of the unknown effects of air pollutants on inflammatory markers during pregnancy and lactation.

A.4.4. **Inclusion/exclusion criteria.** List required characteristics of potential subjects, and those that preclude enrollment or involvement of subjects or their data. Justify exclusion of any group, especially by criteria based on gender, ethnicity, race, or age. If pregnant women are excluded, or if women who become pregnant are withdrawn, specific justification must be provided.

Healthy Individuals

Specific Inclusion Criteria

1. Physical exams will be performed by study physicians during the screening visit (IRB approved EPA protocol 95-EPA-66).
2. Normal lung function (pre or post albuterol), defined by Knudson 1976/1984 as:
   a. FVC of $\geq$ 75 % of that predicted for gender, ethnicity, age and height.
   b. FEV_1 of $\geq$ 75 % of that predicted for gender, ethnicity, age and height.
   c. FEV_1/FVC ratio of $\geq$ 75 % of predicted values.
3. Oxygen saturation of $\geq$ 96 %.
4. Ability to tolerate intervals of moderate exercise

Exclusion Criteria:

1. A history of chronic illnesses such as diabetes, rheumatological diseases, immunodeficiency state, known clinically significant cardiac disease (including myocardial infarction, congestive heart failure and angina), chronic respiratory diseases such as chronic obstructive pulmonary disease, and lung cancer.
2. If the subject is pregnant, attempting to become pregnant or breastfeeding.
3. Allergy to any medications which may be used or prescribed in the course of this study.
4. Subjects currently taking mega doses of vitamins and supplements, homeopathic/naturopathic medicines or medications which may impact the results of the PM and/or ozone challenge or interfere with any other medications potentially used in the study (to include systemic steroids and beta blockers). Subjects must refrain from all over the counter anti-inflammatory agents including those for allergies, and naproxen, and anti-oxidants for a period of one week prior to exposure. Medications not specifically mentioned here may be reviewed by the investigators prior to a subject's inclusion in the study.
5. Smoking history within 2 years of the study.
6. Use of inhaled steroids, cromolyn, or leukotriene inhibitors (Montelukast, Zafirkulast, etc) initiated within the past month (except for use of cromolyn exclusively prior to exercise). Patients must be on a stable regimen of therapy.
7. Untreated hypertension (> 150 systolic, > 90 diastolic)
8. Dementia.
9. Unspecified illnesses, which in the judgment of the investigator might increase the risk associated with PM inhalation challenge or exercise, will be a basis for exclusion.
10. History of skin allergy to tape or electrodes.
11. Subjects who do not understand or speak English
12. Subjects who are unable to perform moderate exercise

Temporary exclusions:

1. Viral upper respiratory tract infection or any acute infection requiring antibiotics within 6 weeks of bronchoscopy.
2. Use of daily medications(at the discretion of physician)

3. Symptom score greater than 20 (out of a possible 60-see accompanying score sheet) for total symptom score with a value greater than 3 for any one score. Only one score may be equal to 3.
4. Current exacerbation of allergic rhinitis and or use of antihistamines during one week prior to exposure.
5. Recent or recurring exposure to pollutants or irritants

Exclusion criteria for bronchoscopy:

1. Any food or fluids after midnight prior to bronchoscopy
2. FEV1/FVC ratio less than 60% predicted on AM of bronchoscopy.
3. Regular use of aspirin $\geq$ 81 mg daily, or other nonsteroidal anti-inflammatory drugs (which inhibit platelet function).

Use of other medications will be evaluated on a case-by-case basis. There is the potential that an individual's current medication use will preclude them from participating in the study at the current time, but they may be reassessed and potentially rescheduled for participation at a later time.

Mild to Moderate Asthmatics

Inclusion Criteria:

1. Physical exams will be performed by study physicians during the screening visit (IRB approved EPA protocol 95-EPA-66) where diagnosis will be judged by EPA physicians.
2. Mild/Moderate asthmatics as defined by NHLBI guidelines.
3. Positive history of asthma (wheezing, chest tightness, and reversible airway obstruction);
4. Baseline $FEV_1/FVC \geq 60\%$;
5. Oxygen saturation of $\geq$ 94%
6. Ability to tolerate moderate exercise

Exclusion Criteria

1. Use of oral steroid therapy within the past month
2. Physician directed emergency treatment for asthma exacerbation within the preceding 6 months.
3. Abnormal EKG that precludes evaluating heart rate variability.
4. Aside from mild/moderate asthma, a history of chronic illnesses such as diabetes, rheumatological diseases, immunodeficiency state, known clinically significant cardiac disease (including myocardial infarction, congestive heart failure and angina), chronic respiratory diseases such as chronic obstructive pulmonary disease or severe asthma, and cancer (possible exception for history of nonmelanoma skin cancer).
5. If the subject is pregnant, attempting to become pregnant or breastfeeding.
6. Allergy to any medications which may be used or prescribed in the course of this study
7. Subjects currently taking mega doses of vitamins and supplements, homeopathic/naturopathic medicines or medications which may impact the results of the PM challenge or interfere with any other medications potentially used in the study (to include systemic steroids and beta blockers). Subjects must refrain from all over the counter anti-inflammatory agents including those for allergies, and naproxen, and anti-oxidants for a period of one week prior to exposure. Medications not specifically mentioned here may be reviewed by the investigators prior to a subject's inclusion in the study.
8. Dosing level of an inhaled steroid must be consistent with mild asthma as outlined by the NHLBI NAEPP guidelines. Regular use of oral corticosteroids, or use of inhaled steroid at doses typically used for severe asthma, will result in exclusion of that individual from the protocol.
9. Severe asthmatics as defined by: nighttime symptoms of cough or wheeze greater than 1 time per week at baseline, daily exacerbation of asthma or requirement for albuterol due to asthma symptoms (cough, wheeze, chest tightness, but not to include prophylactic use of albuterol prior to exercise), more than mild interference with normal activity, any episode of physician directed emergency treatment for asthma requiring oral corticosteroid therapy within the past twelve months.
10. Smoking history within 2 years of study.
11. Use of inhaled steroids, cromolyn, or leukotriene inhibitors (Montelukast, Zafirkulast, etc) initiated within the past month (except for use of cromolyn exclusively prior to exercise). Patients must be on a stable regimen of therapy.
12. History of skin allergy to tape or electrodes.
13. History of respiratory diseases other than allergic rhinitis and asthma
14. Untreated hypertension (> 150 systolic, > 90 diastolic)
15. Dementia.

16. Unspecified illnesses, which in the judgment of the investigator might increase the risk associated with PM inhalation challenge or exercise, will be a basis for exclusion.
17. Subjects who do not understand or speak English
18. Subjects who are unable to perform moderate exercise

Allowances: subjects may
1. Use daily theophylline therapy.
2. Use daily inhaled steroids.
3. Use inhaled cromolyn therapy.

Temporary exclusions:
1. Viral upper respiratory tract infection or any acute infection requiring antibiotics within 6 weeks of bronchoscopy.
2. Use of daily medications(at the discretion of physician)
3. Symptom score greater than 20 (out of a possible 60-see accompanying score sheet) for total symptom score with a value greater than 3 for any one score. Only one score may be equal to 3.
4. Current exacerbation of allergic rhinitis and or use of antihistamines during one week prior to exposure.
5. Recent or recurring exposure to pollutants or irritants

Exclusion criteria for bronchoscopy:
1. Any food or fluids after midnight prior to bronchoscopy
2. FEV1/FVC ratio less than 60% predicted on AM of bronchoscopy.
3. Regular use of aspirin $\geq$ 81 mg daily, or other nonsteroidal anti-inflammatory drugs (which inhibit platelet function).

Use of other medications will be evaluated on a case-by-case basis. There is the potential that an individual's current medication use will preclude them from participating in the study at the current time, but they may be reassessed and potentially rescheduled for participation at a later time.

A.4.5. **Full description of the study design, methods and procedures.** Describe the research study. Discuss the study design; study procedures; sequential description of what subjects will be asked to do; assignment of subjects to various arms of the study if applicable; doses; frequency and route of administration of medication and other medical treatment if applicable; how data are to be collected (questionnaire, interview, focus group or specific procedure such as physical examination, venipuncture, etc.). Include information on who will collect data, who will conduct procedures or measurements. Indicate the number and duration of contacts with each subject; outcome measurements; and follow-up procedures. If the study involves medical treatment, distinguish standard care procedures from those that are research. If the study is a clinical trial involving patients as subjects and use of placebo control is involved, provide justification for the use of placebo controls.

This is a randomized cross-over study with three arms. This study will compare the epigenetic responses of healthy adults and adults with mild asthma to diesel exhaust and ozone exposures. Up to fifty subjects will be recruited into the healthy adult group and up to thirty subjects into the mild to moderate asthmatic group. Subjects will be randomly exposed to clean air, diesel exhaust and ozone with exposures separated by a minimum of two weeks. Responses of primary interest will include: 1) genetic and epigenetic changes 2) FEV1 as measured by spirometry, and 3) lung inflammation and cell changes as evaluated by bronchoalveolar lavage. The performance of these tests and procedures are considered essential to conducting the study. Exploratory endpoints will include: blood CBC and differential, fibrinogen and platelets, changes in IL 6 and IL 8 comparing pre-exposure with post-exposure values. Safety endpoints will include comparison of temperature, telemetry, respiratory rate, O_2 saturation and symptoms scores for pre- and post-exposure, and at 18-24 hours post-exposure. All medical procedures will be performed by study personnel.
Up to an additional 15 healthy subjects will be recruited specifically to be exposed to ozone generated using the heavy non-radioactive isotope of oxygen (18O). There is no risk to the subject of inhaling this isotope, which is naturally occurring in small concentrations. We have previously used 18Ozone in a study approved by the UNC IRB in 1993. The purpose of these exposures is to measure the amount of 18O label attached to airway epithelial cells removed during bronchoscopy and thus calculate the dose of ozone these cells received. We will draw a small

blood sample but no other tests will be performed on these subjects other than routine spirometry to ensure they are not at risk for bronchoscopy.

Physical Examination Day:

Prior to recruitment into the study, subjects will undergo a physical exam. During this visit, a short review of the subject's history will be performed and vital signs, height and weight will be assessed (temperature, pulse, respiratory rate, and blood pressure), to determine whether the individual meets any major exclusion criteria for the study. Up to 50 ml of blood may be collected for a CBC/ differential, chemistry and lipid panels. At this time the subject may undergo a physical examination for bronchoscopy or may be scheduled for one at another time.

In order to participate in this study, subjects will be asked to:

- 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.
- On the Exposure Day 2, eat a normal breakfast.
- No caffeine for 12 hours prior to all study visits.
- At the end of Exposure Day 2, do not eat or drink anything after midnight in preparation for bronchoscopy on Exposure Day 3.

Training Day

1. Eligible subjects will report to the research lab for an approximate 2-hour training session.
2. Informed consent will be obtained.
3. Assessment of **vital signs** (temperature, pulse, respiratory rate, and blood pressure), oxygen saturation
4. **Pregnancy tests** will be administered to any women who may have child-bearing potential.
5. Subjects will be trained on the cycle ergometer and the work load to elicit a minute ventilation normalized for body surface of $25L/m^2/BSA$ will be determined. In most subjects this will be about 50 L/minute (IE. VO^2 of approximately 2.0 L/m). A cycle ergometer work setting of 75 to 100 watts will usually achieve such a physiological response
6. Subjects will perform **spirometry.**
7. Subjects will be shown chamber where exposures will take place.

Exposure Day 1

The subjects will be exposed ozone, diesel exhaust and clean air on three separate occasions, with the exposures separated by a minimum of two weeks. Subjects receiving 18Ozone, will only be exposed to ozone.

1. Subjects will be asked to arrive at the study site no sooner than 8 AM and will undergo **assessment of vital signs** (temperature, pulse, respiratory rate, and blood pressure), oxygen saturation, and **symptom score** assessment.
2. **Pregnancy tests** will be administered to any women who may have child-bearing potential.
3. A **telemetry unit** will be attached for cardiac monitoring.
4. Subject will be fitted with a **Holter monitor** and the subject will be asked to recline in a quiet dark place for 30 minutes. After approximately 20 minutes a time marker will be activated so that heart rate variability frequency readings can be taken over the next 10 minutes. The subject will wear the Holter monitor for the next 24 hrs. Subjects exposed to 18Ozone will not be fitted with a Holter.
5. **Venipuncture:** Up to 80 ml of blood will be collected for a CBC/ differential, and may be used for assessment of coagulation function and markers, phagocytic function, inflammation, and cell surface markers. A portion of the sample may be used for RNA isolation for microarray analysis and for DNA isolation for genotyping purposes. Pre-exposure blood will not be taken from subjects being exposed to 18Ozone
6. **Baseline Spirometry**
7. **Exposure sessions**: Exposure to ozone, diesel exhaust or clean air will be conducted in an exposure chamber at the EPA Human Studies Facility on the UNC campus. Each subject will be exposed up to 0.3ppm ozone, diesel exhaust (up to 300 ug/m^3) or clean air for 2 hours. Subjects will begin exercising on an exercise bike. Each exercise session will consist of a 15 minute exercise interval at a level of up to 25 L/m2/BSA followed by a 15 minute rest period. Minute ventilation may be measured during each exercise

period. Continuous heart rate and rhythm, and oxygen saturation, will be monitored using telemetry and pulse oximetry respectively. Blood pressure may be monitored intermittently. Subjects will be asked to refrain but not prohibited from using inhaled bronchodilator during exposures; if medication use is necessary subjects will be instructed to maintain consistent medication use across the two exposures. The subjects will be able to end their exposure and exit the chamber at any time. Indications for terminating the exposure include significant respiratory distress or dyspnea, chest or angina-like pain, significant cardiac arrhythmias, pallor, ataxia, or a greater than 5 point drop in saturated oxygen (or a drop to lower than 89%). They will be monitored continuously by trained personnel and a physician is on call whenever a subject is undergoing a procedure at the facility. A detailed description of the physical facilities in the Human Studies Division of the U.S. EPA Health Effects Research Laboratory located on the UNC-CH campus have been published as U.S. Government Publication EPA-600/1-78-064, and is on file in the office of the UNC Committee on the Protection of the Rights of Human Subjects. The medical station of the Human Studies Division includes a fully-equipped medical examination room, a cardiac/respiratory emergency cart, a subject recovery room, a nurse's station, a waiting room and conference rooms. The facility is staffed by qualified RNs, and an on-site physician is available to respond to a medical emergency in a timely manner. The exposure atmosphere will be at approximately 40 $\pm$ 10% RH and approximately 22 $\pm$ 2 °C. The DE will be generated from a diesel generator used to power a load bank that is located outside the Human Studies Facility, and subsequently introduced into the exposure chamber after different dilutions with clean HEPA and charcoal filtered and humidified air to give a chamber concentration of up to 300 $\mu g/m^3$. The monitoring analyzer registers a concentration in real time. Exposures will be terminated at values $\geq$ 400 $\mu g/m^3$ during runs in which the exposure targets 300 $\mu g/m^3$ DE. This safety limit will prevent an inhalational exposure greater than 1080 µg, which assumes that the subject will inhale 2.7 m^3 during the 120 min exposure. Levels of carbon monoxide (CO), and oxides of nitrogen (NOx; mainly NO, and some NO_2), will be kept under 10 ppm CO, 15 ppm NO, and 2.5 ppm NO_2 or the exposure will be terminated. [The OSHA 8 hr time-weighted average (TWA) for these substances are: CO=50 ppm; NO=25 ppm; NO_2=5 ppm; Diesel fuel used for the study will be purchased as a commercial ultra low sulfur fuel. Subjects will enter the exposure chamber (about 6 ft x 6 ft x 8 ft). Particle mass will be measured in real time. Particle size distribution may not be determined during each subject exposure but at regular intervals (e.g., monthly) to show that the size distribution does not change radically. Filter samples will also be analyzed for chemical composition of particles. Ozone exposures will be conducted in a (6 ft x 6 ft x 8 ft) stainless steel chamber with a continuous supply of exposure medium. Ozone will be monitored continuously. **Immediately post exposure**, subjects will again undergo **spirometry, Holter monitor frequency reading, symptom scoring and assessment of vital signs.**

8. **Then,** up to 80 ml of blood will be collected for a CBC/ differential, assessment of coagulation function, blood leukocyte phagocytic function, cytokines, cell surface markers and RNA isolation for microarray analysis. Subjects exposed to 18Ozone will have only 20 mls of blood removed for analysis of 18O tag present on blood cells and have post exposure Spirometry measurements.
9. **Subjects exposed to 18Ozone will have bronchoscopy performed about 1 hr post-exposure.** Exposure to 18Ozone and undergoing a bronchoscopy approximately one hour later should not increase the risk to the subjects. We have completed two earlier studies in which subjects underwent bronchoscopy following exposure to concentrations of ozone higher than used in this study, and encountered no problems. Others have also published studies in which subjects were exposed to ozone followed by bronchoscopy one hour later
10. Subjects will then be assessed and discharged by the nursing staff.

Exposure Day 2 (approximately 24 hours after exposure)
Subjects being exposed to 18O will not be returning for a Day 2

The subject will arrive at the U.S. EPA HSF for:

1. **Vital sign monitoring**.
2. **Symptom scoring**.
3. **Venipuncture**: up to 80 ml of blood will be collected for a CBC/ differential, coagulation function, assessment of blood monocyte phagocytic function, inflammation, and cell surface markers, and RNA isolation for microarray analysis.
4. **Holter monitor** frequency reading and removal
5. **Spirometry**

6. **Bronchoscopy.** Subjects will have undergone a physical examination including assessment for suitability for transnasal fiberoptic bronchoscopy at the Human Studies Facility by a board certified or board eligible pulmonologist.

   Prior to the procedure, subjects will perform spirometry (as above); bronchoscopy will not be performed if lung function does not meet the recommended performance level (NIH guidelines; FEV1≥ 60 % predicted). Prior to bronchoscopy, a small tube (IV) will be placed in a vein for potential use in administering fluids. Subjects will receive inhaled albuterol prior to the bronchoscopy at the discretion of the pulmonary physician performing the procedure. Bronchoscopy with bronchoalveolar lavage and brush biopsy will be performed by a licensed physician who is Board certified or board eligible in pulmonary medicine and is experienced in fiberoptic bronchoscopy. The physician will be assisted by at least one R.N experienced in bronchoscopy. The subjects will be monitored closely throughout the procedure in the following manner: 1) Chest electrodes for continuous electrocardiogram, 2) Pulse oximetry of arterial blood, and 3) blood pressure monitoring using an electronic sphygmomanometer. Subjects may be premedicated with IV atropine (0.6 mg) to prevent bradycardia and hypotension that could result from vagal stimulation provoked by passing the bronchoscope through the subject's larynx and to minimize the amount of airways secretions. Nasal oxygen will be administered during the procedure. No sedatives and/or narcotics are administered at any time during bronchoscopy. We have found that premedication with sedatives (midazolam) or with opiates (demerol) is not required for research bronchoscopy subjects. Avoidance of these drugs reduces procedure risk and markedly shortens post-procedure recovery time. Neosynephrine will be used to decongest nasal passages, followed by gargling with a lidocaine solution for a few seconds to anesthetize the throat. The subject will then sniff (snort) a small amount of lidocaine jelly through one nostril to anesthetize the nose and the back of throat. A Q-tip with lidocaine jelly will be gently inserted into the nose to ensure that it is completely numb before the bronchoscope is inserted. Topical lidocaine anesthesia will be administered to the larynx and lower airways through the bronchoscope for subject comfort and to prevent cough, with a maximum dose of 15 ml of 2% lidocaine solution (360 mg lidocaine) Up to 8 endobronchial brush biopsies will be obtained from the lower trachea and right and left mainstem bronchi. A cytology brush (Bronchoscope Cytology Brush; Bard, Tewksbury, MA) is applied to the region under direct visualization. For a single brushing, six passes, each with a linear excursion of approximately 2-5 cm, are made with the brush along the endobronchial surface. Bronchoalveolar lavage will be performed in the right middle lobe using a total volume of up to 250 cc of sterile 0.9% saline; from one to 5 aliquots of 50 cc each will be injected and immediately aspirated through the channel in the bronchoscope using a syringe.

   Subjects are observed and monitored for a minimum of 1 to 2 hours after the procedure in the on-site medical station by a registered nurse with physician supervision. At discharge subjects will be symptom-free. At least 2 physicians, including the responsible bronchoscopist, will be available (24 hours daily) to subjects who develop any symptoms after discharge. The subject is discharged by a physician and is provided with the names and telephone numbers of the bronchoscopist and one other physician. The subject is contacted 24 hours post-bronchoscopy to ask about any untoward effects.

Subjects will return to the U.S. EPA HSF for an additional exposure sessions and post exposure bronchoscopies (air control, ozone or diesel exhaust) after a minimum time interval of two weeks.

We anticipate performing several clinical procedures during the course of this study which include primary, secondary and exploratory endpoints. However, it is possible that not all procedures will be performed on every subject. If we are unable to perform a procedure, because of a investigator problem (such as but not limited too building/equipment failures, weather delays, or staffing issues), then the patient will be compensated for said procedure(s) and time on that day and may be rescheduled.

A.4.6. **Benefits to subjects and/or society.** Describe any potential for direct benefit to individual subjects, as well as the benefit to society based on scientific knowledge to be gained; these should be clearly distinguished. Consider the nature, magnitude, and likelihood of any direct benefit to subjects. If there is no direct benefit to the individual subject, say so here and in the consent form (if there is a consent form). Do not list monetary payment or other compensation as a benefit.

There will be no direct benefit to the subject for participating, other than information that may be learned during their physical examination about their overall physical status. The primary benefit from the study will be to add to the scientific knowledge about whether exposure to air pollutants induces epigenetic changes.

A.4.7. **Full description of risks and measures to minimize risks.** Include risk of psychosocial harm (e.g., emotional distress, embarrassment, breach of confidentiality), economic harm (e.g., loss of employment or insurability, loss of professional standing or reputation, loss of standing within the community) and legal jeopardy (e.g., disclosure of illegal activity or negligence), as well as known side effects of study medication, if applicable, and risk of pain and physical injury. Describe what will be done to minimize these risks. Describe procedures for follow-up, when necessary, such as when subjects are found to be in need of medical or psychological referral. If there is no direct interaction with subjects, and risk is limited to breach of confidentiality (e.g., for existing data), state this.

Risk and Procedures for Minimizing Risks of Diesel Exhaust Exposure

- Diesel Exhaust Exposure: The amount of diesel exhaust used for exposure in this study would be equivalent to concentrations of diesel exhaust particulate matter that would be encountered at busy intersections in large urban area. These concentrations are the occupational levels for some truck drivers (generally about 100-300 $\mu g/m^3$) and 1-2 mg/m^3 for some mines. Some areas of heavily trafficked streets in Los Angeles and New York City have had diesel exhaust levels >20 $\mu g/m^3$, and nearby residents could have exposure to these concentrations over several hours. Controlled diesel exhaust exposure studies in Sweden using 300 $\mu g/m^3$ DEP have shown lung inflammatory effects not unlike effects observed with numerous ozone exposure studies performed here at the EPA facility on the UNC campus during the past 20 yr. Diesel exhaust particles contain some probable carcinogenic polycyclic aromatic hydrocarbons, which in high enough concentrations and/or with repeated exposures may induce tumors. Diesel exhaust also contains aldehydes, some of which are possibly carcinogenic in high enough dose and with long enough exposure. However, the exposure concentrations to be used in this protocol are minimal. Overall, it appears that at the low DEP concentration to be given one time for the exposure in this study, the risk of cancer, if it exists at all, is extremely low and certainly no more than what one would experience if one were to visit for a few days a particulate-polluted city in the US such as Los Angeles or New York City. We have seen in IRB-07-0190 that exposure to 300 $\mu g/m^3$of diesel exhaust does not cause adverse health effects.

Health effects of acute exposures to air pollution particles are not well defined but possibly include chest pain, mild dyspnea, headache, cough, and, in some subjects, wheezing. All of these effects resolve spontaneously within hours of exposure cessation. In the pilot phase of study #07-0190 (Haiyan Tong MD, Ph.D, PI), subjects reported "moderate" eye irritation following diesel exhaust exposure and the symptom was resolved within a few hours after the exposure. Subjects will be provided with the choice to wear chemical safety goggles during exposures to prevent or minimize the eye irritation. During exposure, subjects will be monitored by direct observation or via closed-circuit television. Subjects will have EKG leads attached during the exposure to monitor cardiac function during exercise. Subjects will be aware that they can terminate their exposure for any reason and still receive compensation for their participation up to that point. The investigators or duty physician will end the exposure if the subject is found to be suffering from any significant adverse effect. No major adverse health effects were observed in a recently completed study that exposed subjects (18-35 yr old, healthy volunteers) to concentrated Chapel Hill air particles here at the EPA facility (Physiological and Biochemical Changes Associated with Exposure to Air Pollution Particles; Andrew Ghio, MD, PI; UNC IRB# 95-EPA-310). The maximum PM concentration reached 311 $\mu g/m^3$ during the exposure. The data from this exposure study suggest that normal healthy subjects tolerate inhalation of concentrated ambient PM fairly well, and support the idea that exposures to lower PM concentrations, including DEP, will be fairly safe in terms of cardiopulmonary responses. For safety reasons, pulse oximetry will be performed during the exposures to diesel exhaust and filtered air, and the subject withdrawn from the chamber if the O_2 saturation value is <89%. Additionally subjects will have carboxyhemoglobin values determined within 1 hr after an exposure and kept at the Medical Station if levels are >20% (where performance of everyday cognitive tasks may be jeopardized) until levels become <20%; but because the CO levels are expected to be 2-4 ppm [based on preliminary chamber characterizations], levels are expected to be < 5%.

A duty physician is always onsite to respond to an emergency. Fully equipped resuscitation equipment is available for use in the event of a cardiac or pulmonary emergency. Physicians at the University of North Carolina (UNC) Hospitals Emergency Room are also available to assist in treatment of an emergency.

Heart rate, electrocardiogram, and pulse oximetry will be monitored continuously. Subjects will also be monitored for significant respiratory distress or dyspnea, chest pain, significant cardiac arrhythmias, pallor, and ataxia. Subjects will be aware that they can terminate their exposure for any reason and still receive compensation for the entire exposure session. The investigator or duty physician will end the exposure if the subject is found to be suffering from any adverse effect.

Risk and Procedures for Minimizing Risks of Ozone Exposure

Potential risks may likely include mild airway obstruction, irritation to the nose, eyes, throat and airways, pain on deep inspiration and cough. These symptoms typically disappear 2 to 4 hours after exposure, but may last longer for particularly sensitive people. Ozone may induce an inflammatory reaction that may last for about 24-48 hours after exposure and may increase the chance of catching a cold. It is likely that most subjects participating in this study will experience some degree of tracheobronchial irritation and cough. There is no additional risk associated with the heavy isotope (18O) of ozone.

Risks and Procedures for Minimizing Risks of Venipuncture:

Insertion of the needle may cause minor discomfort at the site of injection and there is a possibility that a bruise will form which may be painful for 2-3 days. It is possible that the subject may feel lightheaded or even faint due to anxiety about the blood draw. Rarely, a skin infection may occur. To minimize these risks, blood is drawn by trained medical professionals. Subjects are closely monitored for any signs of faintness, given liquids and food to eat if requested, and only allowed to leave the facility after a 15-minute waiting period to make sure they are stable.

Risks and Procedures for Minimizing Risks of Bronchoscopy:

The most significant risk to a volunteer in this protocol involves bronchoscopy. Over 1000 procedures have been performed within the EPA Human Studies Facility over the past 15 years. From January 1, 1986 through December 30, 1995, 736 procedures were performed in normal nonasthmatic subjects, and these have been reported in the Journal of Bronchology 1998; 5:185-194. The overall complication rate was less than 1% (actually less than 0.1%). The most frequent complication was a low grade fever. Bronchoscopy with BAL can be associated with more significant complications, including hypoxemia, cough, wheezing, and post-bronchoscopy fever. These may be increased in asthmatic subjects, and some investigators have found hypoxemia to be more severe in asthmatics compared to normal subjects (Djukanović, R., J. W. Wilson, C. K. Lai, S. T. Holgate, and P. H. Howarth. 1991. The safety aspects of fiberoptic bronchoscopy, bronchoalveolar lavage, and endobronchial biopsy in asthma. *Am. Rev. Respir. Dis.* 143: 772-777), while others have not (Van Vyve, T., P. Chanez, J. Bousquet, J. Y. Lacoste, F. B. Michel, and P. Godard. 1992. Safety of bronchoalveolar lavage and bronchial biopsies in patients with asthma of variable severity. *Am. Rev. Respir. Dis.* 146: 116-121); Anonymous. Workshop summary and guidelines: investigative use of bronchoscopy, lavage, and bronchial biopsies in asthma and other airway disease. *J Allergy Clin Immunol* 88:808-14, 1991.;
Jarjour NN, Peters SP, Djukanovic R, Calhoun WJ. Investigative use of bronchoscopy in asthma. Am J Respir Crit Care Med 157:692-97, 1998.) Furthermore, hypoxemia is rarely severe enough to require premature termination of the procedure and can usually be treated or prevented by supplemental oxygen (Van Wyre).

Bronchoscopies are performed by experienced physicians who are either Board-certified or Board-eligible in pulmonary medicine. The physician performing the bronchoscopy is always assisted by at least one nurse familiar with the procedure. The subject's vital signs and ECG are continuously monitored during the bronchoscopic procedures and at regular intervals during the recovery phase. The procedure is immediately terminated if the subject experiences any alterations such as tachypnea, depressed respiration, tachycardia, bradycardia, abnormal rhythms or significant changes in blood pressure. As indicated earlier, a fully equipped emergency cart including a defibrillator, endotracheal intubation equipment and emergency medications (atropine, epinephrine) is available at all times. An on-site physician is always available to respond and the UNC Memorial Hospital Emergency Room is within 1/4 mile of Human Studies Facility. Before the subject is sent home, he/she receives a brief physical examination by a physician and is given phone numbers and a pager number with which to contact a physician should he/she experience any problems or have any questions.

The complication rate during medical bronchoscopy is approximately 0.08 to 0.12% for all events, including low oxygen saturation, respiratory embarrassment, myocardial infarction, or death. The medical screening of the subjects is specifically designed to exclude subjects with a history of medical problems which might put them at risk from the particle exposure and bronchoscopic procedures. Medical problems which could arise as a result of bronchoalveolar lavage and brush biopsy include the following:

Discomfort of the nose and throat is a primary risk of bronchoscopy. As outlined, the lidocaine gargle, spray and liquid is used to anesthetize these areas prior to passing the bronchoscope to reach the lower airways. The procedure will be discontinued if adequate anesthesia cannot be achieved by the means described.

Low-grade fever (38-38.5 °C) can occur in approximately 25 % of hospitalized subjects undergoing bronchoscopy. The fever invariably resolves within 18 hours without treatment or with acetaminophen. Our experience at HSD, EPA has shown that this fever and the associated malaise can almost always be prevented by administering ibuprofen following the procedure. The subject will be asked to contact the physician who performed the procedure or one of the nurses at the Medical Station if fever persists or is higher than 38.5 °C. As part of the standard protocol, a nurse or physician will contact the subject by telephone between 24 and 48 hours after the procedure to inquire on the general health of the subject and specifically about the presence of fever.

Cough is a common, albeit minor, problem encountered during bronchoscopy. Cough results from mechanical stimulation of cough receptors in the airway by the bronchoscope or the cytologic brush used for the brush biopsies. In addition to the discomfort, prolonged coughing with the bronchoscope in place can result in mild mechanical trauma to the vocal cords. Lidocaine solution is passed through the bronchoscope channel at the main carina and at the level of the right mainstream bronchus to suppress the cough reflex during the procedure, more can be used as needed. The procedure will be terminated if adequate cough suppression cannot be attained.
Epistaxis is caused by trauma to the nose by the bronchoscope. This condition is expected to be minor and resolve on its own. Small streaks of blood in nasal secretions may be present for up to 12 hours following the procedure. If the bleeding becomes moderate or severe during bronchoscopy, the procedure will be terminated and the bronchoscope removed. The subject's anterior nasal passage will be packed with sterile gauze to stop the bleeding. If the bleeding does not resolve with packing, the subject will be transferred to the UNC Hospital Emergency Room.
Lidocaine use presents a small risk to the subjects, as a variable fraction of the medication is absorbed through the airway mucosa. If a significant amount of lidocaine is absorbed, adverse reactions such as bradycardia, hypotension, urticarial reactions, confusion, lightheadedness, euphoria, tremors and seizures can result. We take particular precautions to avoid the possibility of overdose of topical lidocaine and limit the total amount of lidocaine instilled into the airways to a maximum of 360 mg. Also, subjects will be screened by history prior to the procedure for known allergies to lidocaine or other similar topical anesthetics.
Bronchospasm, manifested as wheezing, chest tightness or dyspnea, is a risk of bronchoscopy that is caused by stimulation of irritant receptors in the airways by the bronchoscope. This risk is minimized by 1) only allowing persons with stable mild to moderate stable asthma to participate in the study, 2) pretreatment with inhaled bronchodilator before the procedure per request of the bronchoscopy physician 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 physicians responsible for the procedure. Administration of inhaled bronchodilator (albuterol) is all that should be required to control the symptoms. In the unlikely event that the subject requires additional treatment because the asthma attack continues, they will be transported by ambulance to the emergency room of the UNC Hospital Emergency Room.
Pneumothorax is a risk of bronchoscopic procedures such as transbronchial biopsy, peripheral lung protected brushings or peripheral lung cytology brushings. Because these procedures will not be performed, the risk of pneumothorax in this study is extremely small. There is a very small risk of a pneumothorax resulting from a endobronchial brush biopsy. The symptoms include dyspnea and chest pain. The subjects will be interviewed and examined by the bronchoscopy physician 2 hours after the procedure with these symptoms in mind. If a pneumothorax is suspected, the subject will be transferred to the UNC Hospital Emergency Room by ambulance for further evaluation and treatment.
Bleeding in the lower airway may occur from trauma caused by the bronchoscope or by brush biopsy. Bleeding is typically very minor, in the order of 1/10 cc, is not clinically significant in an otherwise healthy subject and should spontaneously resolve in a matter of minutes. Epinephrine, diluted 1/20,000 fold will be administered through the bronchoscope to the affected site if bleeding is minor to moderate. The maximum dose of epinephrine used will be 2-3 cc to prevent local tissue necrosis. The site will be monitored through the bronchoscope until the bleeding stops. If bleeding fails to resolve with epinephrine or if it is sufficiently severe to cause hemoptysis or hemoglobin desaturation, oxygen supplementation will be provided to keep arterial oxygen saturation above 90% and the subject will be transported to the NC Memorial Hospital Emergency Room by ambulance. If it becomes necessary, the subject can be intubated before transport.

The use of epinephrine to control bleeding can produce systemic effects resulting from mucosal absorption of the drug. These symptoms are transient and include headache, palpitations and tachycardia when the dose is greater than 1 mg and is given intravenously. Two cc of a 1/20, 000 dilution of epinephrine contains 0.10 mg of the drug, a dose that is very unlikely to induce any untoward effects. This is especially true when the drug is applied to the mucosa, since only a fraction is expected to be absorbed.
Bradycardia and/or hypotension may result from increased vagal nerve output provoked by coughing or Valsalva during the passage of the bronchoscope through the vocal cords and trachea. Atropine (0.6 mg iv) is prophylactically administered to the subjects before the start of the procedure to minimize this risk. The primary side effects associated with atropine administration is mild sinus tachycardia which typically resolves within 30 minutes as the drug is cleared from the subject's system. In rare cases (less than 1 percent) the sinus tachycardia is accompanied by hypotension.
Hypoxemia: Arterial blood oxygen saturation is continuously monitored during the procedure with a finger pulse oximeter. Subjects are supplemented with oxygen at a flow rate of 2 l/min via nasal cannula during the procedure. The oxygen flow can be increased to a maximum of 6 l/min if the arterial oxygen saturation falls below 93 %. If oxygen supplementation is not effective, the procedure will be discontinued immediately. Removal of the bronchoscope and treatment with inhaled bronchodilator should be sufficient to allow the subject's arterial oxygen saturation to return to normal. Under normal conditions, oxygen supplementation is ceased once the procedure is completed. However, supplementation will be continued if arterial oxygen saturation is below 93 % on room air. In

the event that low oxygen saturation persists, if the subject cannot be weaned from the oxygen supplementation, or if it falls precipitously at any time, an emergency situation will be declared and the subject will be transported immediately by ambulance to the UNC Hospital Emergency Room. These risks are minimized during the research procedure at the Human Studies Facility, in part because premedication with sedatives (midazolam) or with opiates (demerol) (as is used in medical bronchosopy) is not required for healthy research subjects. Avoiding these drugs reduces procedure risk and allows the participants to enjoy a normal day after leaving the EPA Human Studies Facility.

The risk of pneumonia as a result of bronchoalveolar lavage in the lobe involved in the procedure is less than 1%. Symptoms of pneumonia could include fever, dyspnea, persistent cough, productive cough and chest pain. The subject will be instructed to call the physician who performed the procedure or the Medical Station if these symptoms occur. The medical staff will evaluate the subject over the phone between 24 and 48 hours after the procedure for signs of pneumonia.

The subject will be urged to contact the Medical Station or the bronchoscopy physician should he/she experience any of the following symptoms: 1) Epistaxis, 2) Persistent cough, 3) Hemoptysis, 4) Chest pain, 5) Dyspnea, 6) Wheezing, 7) Sputum production, 8) Hoarseness or sore throat.

Confidentiality Risk

Risk of breach of confidentiality is minimal. For the mild asthmatic subject, it is conceivable that an employer or insurance company could learn of the diagnosis if the subject requires medical intervention as a result of participating in the study. All subjects will be assigned a study number which will be used for data recording – not the subject's name. The study number is all that will be entered into computer databases. All paper files which may contain the subject's name or screening number are secure in the EPA building which has limited access 24 hours/day. Any abnormal medical findings (CBC, ECG, spirometry) will be discussed with the subject and the subject will be counseled to seek treatment from his/her personal physician if indicated. Samples will be stored at the U.S. EPA HSF. A numeric coding system will be used to ensure that subjects cannot be directly identified from the samples alone.

A.4.8. **Data monitoring and analysis.** Tell how the qualitative and/or quantitative data will be analyzed. Explain how the sample size is sufficient to achieve the study aims. This might include a formal power calculation or explanation of why a small sample is sufficient (e.g., qualitative research, pilot studies). Describe the provisions for monitoring the data to ensure the safety of participants. These plans could range from the investigator monitoring subject data for any safety concerns to a sponsor-based DSMB, depending on the study.

The research objective of this study is to determine if changes in epigenetic mechanisms in bronchial epithelial cells can be linked to physiological changes in healthy and mild/moderate asthmatic volunteers safely exposed to low levels of O3 and diesel exhaust. The study will follow a randomized, repeated measures design with each subject exposed to clean air, diesel exhaust and ozone. The data analysis will be focused on changes in lung function measurements, primarily FVC and FEV_1, and secondarily, HRV measurements between pre and post 2hr exposure for each exposure and lung cell composition changes. Also blood endpoints include inflammatory factors (eg IL-6), blood clotting factors (eg fibrinogen), and susceptibility factors (eg specific genotypes associated with susceptibility to air pollution).

In evaluating exposure effects of O3 and DE upon lung function, the difference between the pre-exposure and post-exposure FEV1 will be calculated and the pre-post differences for the air and the exposures will be compared utilizing repeated measures ANOVA parametric test. Clinically significant change is determined to be a 10% decrease in FEV1 measured prior to and immediately after the exposure compared to the pre exposure value. For a conservative sample size calculation, we used one sided test for a single sample under the assumption of normal distribution with Type I error of 5% and Type II error of 20%. Therefore, a ρ value of 0.05 or less will be considered significant and the proposed sample size will provide adequate (80%) power for detecting a 10% decrease in ΔFEV1.

Sample size calculation was based on the Forced Expiratory Volume in 1 Second (FEV1) in response to the O3 exposure. Data for the power calculation were obtained from results of FEV_1 (Folinsbee, Bedi et al. 1985) for a constant acute exposure to 0.3 ppm O_3 versus filtered air. In 22 subjects, the pre exposure FEV_1 was 4.608 ± 0.514 (mean $\pm$ SEM) in FA exposure and 4.656 ± 0.592 in O_3. The post exposure FEV_1 was 4.64 ± 0.476 in FA exposure and 3.856 ± 0.687 in O_3. We used 0.687 as an estimate of standard deviation after the ozone exposure and estimated 10% decrease in pre-exposure FEV1 levels to be 0.46 ml. Based on these data the required sample size for each

group is 30 subjects. We will initially recruit 30 subjects for each group (healthy and mild/moderate asthmatics) for this study to ensure the statistical power that can analyze small differences expected from low concentration exposures.

Other Exploratory Observations:
We hypothesize that subjects harboring polymorphisms in antioxidant genes will have increased responses to diesel exhaust and ozone compared to subjects who do not. In order to address this we will use collected cell samples for in vitro exposure experiments

Exploratory endpoints will include the effect of diesel exhaust and ozone on changes in: blood CBC and differential, fibrinogen and platelets, changes in IL 6 and IL 8 comparing pre-exposure with post-exposure values.

A.4.9. **Will you collect or receive any of the following identifiers?** Does not apply to consent forms.

__ No _X_ Yes *If yes, check all that apply:*

a. _X_ Names
b. _X_ Telephone numbers
c. _X_ Any elements of dates (other than year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death. For ages over 89: all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 and older
d. _X_ Any geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code
e. __ Fax numbers
f. _X_ Electronic mail addresses
g. __ Social security numbers
h. _X_ Medical record numbers
i. __ Health plan beneficiary numbers
j. __ Account numbers
k. __ Certificate/license numbers
l. __ Vehicle identifiers and serial numbers (VIN), including license plate numbers
m. __ Device identifiers and serial numbers (e.g., implanted medical device)
n. __ Web universal resource locators (URLs)
o. __ Internet protocol (IP) address numbers
p. __ Biometric identifiers, including finger and voice prints
q. __ Full face photographic images and any comparable images
r. __ Any other unique identifying number, code, or characteristic, other than dummy identifiers that are not derived from actual identifiers and for which the re-identification key is maintained by the health care provider and not disclosed to the researcher

A.4.10. **Identifiers in research data**. Are the identifiers in A.4.9 above linked or maintained with the research data?

_X_ yes __ no

A.4.11. **Confidentiality of the data**. Describe procedures for maintaining confidentiality of the data you will collect or will receive. Describe how you will protect the data from access by those not authorized. How will data be transmitted among research personnel? Where relevant, discuss the potential for deductive disclosure (i.e., directly identifying subjects from a combination of indirect IDs).

No personal identifying information will be attached to the samples. No subjects will be identified in any report or publication about this study. Study samples will be stored in a secure room with restricted access. The sample will be prepared and stored indefinitely in a freezer for future testing. Portions of the sample may be shared with researchers at other scientific institutions or sent to outside clinical laboratories for analysis, however, only coded samples will be sent. All medical records generated during this study will be kept in a locked file cabinet in the Medical Station at the U.S. EPA 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 a day for seven days a week

A.4.12. **Data sharing.** With whom will *identifiable* (contains any of the 18 identifiers listed in question A.4.9 above) data be shared outside the immediate research team? For each, explain confidentiality measures. Include data use agreements, if any.

_X_ No one
__ Coordinating Center:
__ Statisticians:
__ Consultants:
__ Other researchers:
__ Registries:
__ Sponsors:
__ External labs for additional testing:
__ Journals:
__ Publicly available dataset:
__ Other:

A.4.13. **Data security for storage and transmission**. Please check all that apply.

For electronic data stored on a desk top computer:
_X_ Secure network _X_ Password access __ Data encryption__ Password protected file(s)
__ Other comparable safeguard (describe):

For portable computing devices/external storage devices (e.g. laptop computer, PDA, CDs, memory sticks):
__ Power-on password __ Automatic log-off __ Data encryption __ Password protected file(s)
__ Other comparable safeguard (describe):

For hardcopy data (including human biological specimens, CDs, tapes, etc.):
__ Data de-identified by research team (stripped of the 18 identifiers listed in question A.4.9 above)
__ Locked suite or office _X_ Locked cabinet
__ Data coded by research team with a master list secured and kept separately
__ Other (describe):

A.4.14. **Post-study disposition of identifiable data or human biological materials**. Describe your plans for disposition of data or human biological specimens that are identifiable in any way (directly or via indirect codes) once the study has ended. Describe your plan to destroy identifiers, if you will do so.

Samples will be stored in a repository where only project members of the study will have access to the samples. Subjects at any time may request that their samples be no longer stored in the repository. Any analysis in progress at the time of the request or already performed prior to the request being received by the researcher will continue to be used as part of the research study. Once the researcher is notified, the subject's specimens will be destroyed.

Part A.5. The Consent Process and Consent Documentation (including Waivers)

The standard consent process is for all subjects to sign a document containing all the elements of informed consent, as specified in the federal regulations. Some or all of the elements of consent, including signatures, may be altered or waived under certain circumstances.

- If you will obtain consent in any manner, complete **section A.5.1**.
- If you are obtaining consent, but requesting a waiver of the requirement for a signed consent document, complete **section A.5.2**.
- If you are requesting a waiver of any or all of the elements of consent, complete **section A.5.3**.
- If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a *limited waiver of HIPAA authorization*. This is addressed in section B.2.

You may need to complete more than one section. For example, if you are conducting a phone survey with verbal consent, complete sections A.5.1, A.5.2, and possibly A.5.3.

A.5.1. **Describe the process of obtaining informed consent from subjects.**
Describe who will be obtaining consent (or permission) and from whom. Include discussion, as relevant, any waiting period between the initial consent discussion and obtaining consent, and steps that will be taken to minimize coercion or undue influence. If children will be enrolled as subjects, describe the provisions for obtaining parental permission and assent of the child. If decisionally impaired adults are to be enrolled, describe the provision for obtaining surrogate consent from a legally authorized representative (LAR). If non-English speaking people will be enrolled, explain how consent in the native language will be obtained. Address both written translation of the consent and the availability of oral interpretation. It is expected that the information in the consent document(s) will be communicated to participants or their LAR. *After you have completed this part A.5.1, if you are not requesting a waiver of any type, you are done with Part A.5.; proceed to Part B.*

The subject will be given an opportunity to read the consent form. At that time a member of the study team (usually the PI) will verbally describe the study and the subject will have an opportunity to ask questions or address concerns about any aspect of the study. The subject will be given a copy of the signed consent form for his/her records.

A.5.2. **Justification for a waiver of *written* (i.e., signed) consent**. *The default is for subjects to sign a written document that contains all the elements of informed consent.* Under limited circumstances, the requirement for a signed consent form may be waived by the IRB if either of the following is true. *Choose only one:*

a. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., study topic is sensitive so that public knowledge of participation could be damaging). *Participants should be asked whether they want documentation linking them with the research and the participants' wishes will govern whether they sign the form.* Note: This justification cannot be used in FDA-regulated research. __ yes __ no __ yes __ no
Explain.

b. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (e.g., phone survey).
Explain.

If you checked "yes" to either (and you are not requesting a waiver in section A.5.3) consent must be obtained orally, by delivering a fact sheet, through an online consent form, or be incorporated into the survey itself. Include a copy of the consent script, fact sheet, online consent form, or incorporated document.

→ If you have justified a waiver of written (signed) consent (A.5.2), you should complete A.5.3 *only* if your consent process will not include all the other elements of consent.

A.5.3. **Justification for a full or partial waiver of consent.** *The default is for subjects to give informed consent.* A waiver might be requested for research involving only existing data or human biological specimens (see also Part C). More rarely, it might be requested when the research design requires withholding some study details at the outset (e.g., behavioral research involving deception). In limited circumstances, parental permission may be waived. This section should also be completed for a waiver of HIPAA authorization if research involves Protected Health Information (PHI) subject to HIPAA regulation, such as patient records.

__ Requesting **waiver of some elements** (specify; see SOP 28 on the IRB web site):
__ Requesting **waiver of consent entirely**

If you check either of the boxes above, answer items a-f.. To justify a full waiver of the requirement for informed consent, you must be able to answer "yes" (or "not applicable" for question c) to items a-f. **Insert brief explanations that support your answers.**

a. Will the research involve no greater than minimal risk to subjects or to their privacy? __ yes __ no
Explain.

b. Is it true that the waiver will *not* adversely affect the rights and welfare of subjects? *(Consider the right of privacy and possible risk of breach of confidentiality in light of the information you wish to gather.)* __ yes __ no
Explain.

c. When applicable to your study, do you have plans to provide subjects with pertinent information after their participation is over? *(e.g., Will you provide details withheld during consent, or tell subjects if you found information with direct clinical relevance? This may be an uncommon scenario.)* __ yes __ not applicable
Explain.

d. Would the research be impracticable without the waiver? *(If you checked "yes," explain how the requirement to obtain consent would make the research impracticable, e.g., are most of the subjects lost to follow-up or deceased?).* __ yes __ no
Explain.

e. Is the risk to privacy reasonable in relation to benefits to be gained or the importance of the knowledge to be gained? __ yes __ no
Explain.

If you are accessing patient records for this research, you must also be able to answer "yes" to item f to justify a waiver of HIPAA authorization from the subjects.

f. Would the research be impracticable if you could not record (or use) Protected __ yes __ no

Health Information (PHI)? *(If you checked "yes," explain how* not *recording or using PHI would make the research impracticable).*
Explain.

Part B. Questions for Studies that Involve Direct Interaction with Human Subjects

→ ***If this does not apply to your study, do not submit this section.***

B.1. **Methods of recruiting.** Describe how and where subjects will be identified and recruited. Indicate who will do the recruiting, and tell how subjects will be contacted. Describe efforts to ensure equal access to participation among women and minorities. Describe how you will protect the privacy of potential subjects during recruitment. *For prospective subjects whose status (e.g., as patient or client), condition, or contact information is not publicly available (e.g., from a phone book or public web site), the initial contact should be made with legitimate knowledge of the subjects' circumstances. Ideally, the individual with such knowledge should seek prospective subjects' permission to release names to the PI for recruitment. Alternatively, the knowledgeable individual could provide information about the study, including contact information for the investigator, so that interested prospective subjects can contact the investigator.* Provide the IRB with a copy of any document or script that will be used to obtain the patients' permission for release of names or to introduce the study. Check with the IRB for further guidance.

Subjects will be recruited for this study by the Westat Corporation, which has recruited for studies at the U.S EPA HSF since 1998. The manner in which this will be done is similar that that of past U.S. EPA studies and specific recruitment procedures as per the previously UNC IRB-approved protocol, Recruitment and Screening of Potential Subjects for U.S. EPA Studies (95-EPA-66). Typical methods for recruiting may include mass mailings, fliers and print ads. Every effort will be made to recruit women and members of racial minority groups into this study. Subjects will be asked to call the recruitment office. During the telephone interview, the subjects will receive information regarding the study and their eligibility for the study will be assessed. Subjects who provide responses which indicate that they are likely to meet the criteria will be scheduled for an appointment in the Westat recruitment office in the U.S. Human Studies Facility. At that time the study protocol will be outlined, and a medical history form will be administered.

B.2. **Protected Health Information (PHI).** If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a *limited waiver of HIPAA authorization*. If this applies to your study, please provide the following information and complete Section C.

a. Under this limited waiver, you are allowed to access and use only the minimum amount of PHI necessary to review eligibility criteria and contact potential subjects. What information are you planning to collect for this purpose?

b. How will confidentiality/privacy be protected prior to ascertaining desire to participate?

c. When and how will you destroy the contact information if an individual declines participation?

B.3. **Duration of entire study and duration of an individual subject's participation, including follow-up evaluation if applicable.** Include the number of required contacts and approximate duration of each contact.

It is anticipated that the duration of this study will be approximately eighteen months. Subject recruitment and screening is expected to be continuous throughout the study until the intended number of subjects is reached. Scheduling constraints imposed by concurrent studies in the U.S. EPA Human Studies Division are expected to limit the rate at which subjects can be exposed to 1-2 per week.

The physical examination evaluation may take up to one hour. If the subject is eligible for the study, the individual may have up to nine more visits to the research facility over approximately 6 months. A physical examination for bronchoscopy will be performed. The training day visit will require approximately 2 hours. Exposure day (Day 1) will last approximately 6 hours. Subjects will report to the facility at no sooner than 8 AM. The morning following the exposure, the subject will return for Day 2 which is a follow-up visit and may last approximately 4 hours. Subjects will report to the facility at no sooner than 8 AM. Subjects will then return and repeat the Day 1-2 visits with the second and third exposure session. Exposure sessions will be separated by a minimum of two weeks.

B.4. **Where will the subjects be studied?** Describe locations where subjects will be studied, both on and off the UNC-CH campus.

Subjects will be seen in the U.S. EPA Human Studies Facility on Mason Farm Road in Chapel Hill.

B.5. **Privacy.** Describe procedures that will ensure privacy of the subjects in this study. Examples include the setting for interviews, phone conversations, or physical examinations; communication methods or mailed materials (e.g., mailings should not indicate disease status or focus of study on the envelope).

All interviews, phone conversations, and physical examinations will be conducted in private rooms in the U.S. EPA Human Studies Facility. This facility is guarded and only individuals working in the building have access beyond the guard's desk without an escort

B.6. **Inducements for participation.** Describe all inducements to participate, monetary or non-monetary. If monetary, specify the amount and schedule for payments and if/how this will be prorated if the subject withdraws (or is withdrawn) from the study prior to completing it. For compensation in foreign currency, provide a US$ equivalent. Provide evidence that the amount is not coercive (e.g., describe purchasing power for foreign countries). Be aware that payment over a certain amount may require the collection of the subjects' Social Security Numbers. If a subject is paid more than $200.00 per year, collection of subjects' Social Security Number is required (University policy—see SSN Guidance) using the Social Security Number collection consent addendum found under forms on the IRB website (look for Study Subject Reimbursement Form).

Subjects will receive monetary compensation for their time (approximately $12 per hour) and procedures in the study. In addition, subjects traveling from areas beyond Chapel Hill/Carrboro will be reimbursed for travel expenses commensurate with the US Government mileage rate in effect at the time. Parking will be provided or costs will be paid. Payments will be made after each segment of the study, unless the subject requests otherwise.

A subject who is unable to complete the study for voluntary reasons or failure to comply with eligibility requirements will receive full compensation for his/her participation up to that point. Subjects who are dismissed by the investigators for involuntary reasons after enrollment in the study but prior to completion will be paid for their participation up to that point

In the event a scheduled study activity must be cancelled by the investigators with less than 72 hours prior notice, the subject will be paid at the standard hourly rate for the time scheduled and for any procedures cancelled up to a maximum of $100. Cancellations could occur due to adverse weather conditions, equipment failure, or other unforeseen events. When feasible, the subject will be rescheduled.

The following table details the expected compensation for completion of the entire study:
Subjects will be paid approximately $12 per hour for participation in this study. If the subjects complete all three exposures with bronchoscopy, the total compensation including prestudy qualifications will be approximately $2516.

Pre-study qualifications

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

Pre-study qualification total = $50

Training Day (approximately 2 hours)

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

Training Day Total = $ 44

Subjects 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 **$1548**

TOTAL for completion of THREE exposures (including completion bonus) **$2422**

If a subject begins but cannot complete the bronchoscopy procedure for voluntary or involuntary reasons, they will receive compensation for participation up to that point.

Subjects will be asked to bring a lunch for the exposure day and a refrigerator and microwave will be available. If a subject is terminated from the study or chooses to withdraw he/she will be reimbursed for time and procedures completed up to that time point.

B.7. **Costs to be borne by subjects.** Include child care, travel, parking, clinic fees, diagnostic and laboratory studies, drugs, devices, all professional fees, etc. If there are no costs to subjects other than their time to participate, indicate this.

There will be no cost to the subject. Subjects traveling from areas beyond Chapel Hill/Carrboro will be reimbursed for travel expenses commensurate with the U.S. Government mileage rate in effect at the time. Parking will be provided or costs will be paid. Payments will be made after each segment of the study, unless the subject requests otherwise.

Part C. Questions for Studies using Existing Data, Records or Human Biological Specimens

→ ***This section applies even if records are only used to identify potential subjects.***

→ ***If your study does not use existing data, records or specimens for any purpose, do not submit this section.***

C.1. What records, data or human biological specimens will you be using? *(check all that apply)*:

__ Data already collected for another research study
If applicant was involved in the original collection, please explain role:

__ Data already collected for administrative purposes (e.g., Medicare data, hospital discharge data)
__ Medical records (custodian may also require form, e.g., HD-974 if UNC-Health Care System)
__ Electronic information from clinical database (custodian may also require form)
__ Patient specimens (tissues, blood, serum, surgical discards, etc.)
__ Other (specify):

C.2. For each of the boxes checked in 1, how were the original data, records, or human biological specimens collected? Describe the process of data collection including consent, if applicable.

C.3. For each of the boxes checked in 1, where do these data, records or human biological specimens currently reside?

C.4. For each of the boxes checked in 1, do you have permission from the custodians of the data, records or human biological specimens (e.g., pathology dept, tissue bank, original researcher)? Include data use agreements, if required by the custodian of data that are not publicly available.

C.5. If the research involves human biological specimens, has the purpose for which they were collected been met before removal of any excess? For example, has the pathologist in charge or the clinical laboratory director certified that the original clinical purpose has been satisfied? Explain if necessary.

__ yes __ no __ not applicable (explain)

C.6. Do *all* of these data, records or specimens exist at the time of this application? If not, explain how prospective data collection will occur.

__ yes __ no If no, explain

SUBJ #_____ DATE_____

SYMPTOM QUESTIONNAIRE FOR CHAMBER EXPOSURE STUDIES

Pre-Exposure / End Exposure / 24 hrs post end Exposure (Circle one)

INSTRUCTIONS: Please indicate if you are experiencing any of the symptoms or restrictions listed below, using the following scale to indicate the severity. Circle the number.

0 = NONE (not present)
1 = TRACE/NOTICED (barely detectable)
2 = MILD/LIGHT (present, but not annoying)
3 = MODERATE (present, but somewhat annoying)
4 = SEVERE/HEAVY (present and very annoying and painful)

SYMPTOMS	NONE	TRACE	MILD	MODERATE	SEVERE
1. HEADACHE	0	1	2	3	4
2. IRRITATION OF THE NOSE	0	1	2	3	4
3. STUFFY NOSE/SINUS CONGESTION	0	1	2	3	4
4. RUNNY NOSE	0	1	2	3	4
5. DRY/SORE THROAT	0	1	2	3	4
6. PAIN on DEEP INSPIRATION	0	1	2	3	4
7. UNUSUAL FATIGUE OR TIREDNESS	0	1	2	3	4
8. EYE IRRITATION	0	1	2	3	4
9. SHORTNESS OF BREATH	0	1	2	3	4
10. SNEEZING	0	1	2	3	4
11. COUGH	0	1	2	3	4
12. WHEEZING/WHISTLING in CHEST	0	1	2	3	4
13. CHEST TIGHTNESS	0	1	2	3	4
14. SWEATING	0	1	2	3	4
15. Other_____	0	1	2	3	4

Fw: IRB Notice
Deepika Polineni to: Mike Schmitt 11/02/2012 03:36 PM

From: Deepika Polineni/RTP/USEPA/US
To: Mike Schmitt/RTP/USEPA/US@EPA

---- Forwarded by Deepika Polineni/RTP/USEPA/US on 11/02/2012 03:36 PM ----

From: Howard Kehrl/RTP/USEPA/US
To: Deepika Polineni/RTP/USEPA/US@EPA
Date: 09/29/2011 01:53 PM
Subject: Fw: IRB Notice

---- Forwarded by Howard Kehrl/RTP/USEPA/US on 09/29/2011 01:53 PM ----

From: IRB <irb_no_reply@mailserv.grad.unc.edu>
To: David Diaz-Sanchez/RTP/USEPA/US@EPA
Cc: mschmitt@email.unc.edu, keduncan@email.unc.edu, Kelly Duncan/RTP/USEPA/US@EPA, Howard Kehrl/RTP/USEPA/US@EPA
Date: 09/28/2011 02:14 PM
Subject: IRB Notice

TO: David Diaz Sanchez
Environmental Protection Agency
7315

FROM: Biomedical IRB

DATE: 9/28/2011

RE: Notice of Receipt of Modification Submission on 9/28/2011
STUDY #: 09-1625

STUDY TITLE: Epigenetic Effects of Diesel Exhaust and Ozone Exposure

Your submission for the above-referenced study has been received by the Office of Human Research Ethics and will be reviewed by the appropriate IRB.

Please refer to the above study number when corresponding with our office about this study.

If this is an initial application and you disclosed any potential conflict of interest in "Part A.3" it must be resolved with the COI review committee before your study can be reviewed by the IRB. Further information can be obtained at http://coi.unc.edu or 919.843.9953.

All other questions about your submission should be directed to 919.966.3113.

CC:
Michael Schmitt, Epa
Kelly Duncan, Enviro Med Asthma And Lung Bio
Duncan Kelly
Howard Kehrl, (EPA), Non-IRB Review Contact

IRB Informational Message—please do not use email REPLY to this address

Fw: IRB Notice
Deepika Polineni to: Mike Schmitt 11/02/2012 04:00 PM

From: Deepika Polineni/RTP/USEPA/US
To: Mike Schmitt/RTP/USEPA/US@EPA

---- Forwarded by Deepika Polineni/RTP/USEPA/US on 11/02/2012 04:00 PM ----

From: IRB <irb_no_reply@mailserv.grad.unc.edu>
To: David Diaz-Sanchez/RTP/USEPA/US@EPA
Cc: mschmitt@email.unc.edu, keduncan@email.unc.edu, keduncan@email.unc.edu, Deepika Polineni/RTP/USEPA/US@EPA
Date: 10/18/2011 01:20 PM
Subject: IRB Notice

To: David Diaz Sanchez
Environmental Protection Agency
CB#: 7315

From: Biomedical IRB

Approval Date: 10/18/2011
Expiration Date of Approval: 8/20/2012

RE: Notice of IRB Approval by Full Board Review
Submission Type: Modification
Study #: 09-1625

Study Title: Epigenetic Effects of Diesel Exhaust and Ozone Exposure
Sponsors: US Environmental Protection Agency - GRANTS

This submission has been approved by the above IRB for the period indicated. Unless otherwise noted, regulatory and other findings made previously for this study continue to be applicable.

Submission Description:

This amendment received 9/28/11 addresses the addition of a second arm to assess the genetic and epigenetic changes to the lung cells of healthy volunteers 1 hour following exposure to ozone.

Investigator's Responsibilities:

IF YOU SUBMITTED ON PAPER, enclosed are stamped copies of approved consent documents and other recruitment materials (when applicable). You must copy the stamped consent forms for use with subjects unless you have approval to do otherwise. **IF YOU**

SUBMITTED ONLINE (Behavioral and Public Health-Nursing IRBs Only), your approved consent forms and other documents are available online at http://apps.research.unc.edu.

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40 CFR 26 (EPA), where applicable.

CC:
Michael Schmitt, Epa
Kelly Duncan, Enviro Med Asthma And Lung Bio
Kelly Duncan, Enviro Med Asthma and Lung Bio
Deepika Polineni, (EPA), Non-IRB Review Contact

IRB Informational Message—please do not use email REPLY to this address

Fw: IRB Notice
Deepika Polineni to: Mike Schmitt 11/02/2012 03:57 PM

From: Deepika Polineni/RTP/USEPA/US
To: Mike Schmitt/RTP/USEPA/US@EPA

---- Forwarded by Deepika Polineni/RTP/USEPA/US on 11/02/2012 03:57 PM ----

From: IRB <irb_no_reply@mailserv.grad.unc.edu>
To: David Diaz-Sanchez/RTP/USEPA/US@EPA
Cc: mschmitt@email.unc.edu, keduncan@email.unc.edu, keduncan@email.unc.edu, Deepika Polineni/RTP/USEPA/US@EPA
Date: 10/28/2011 01:27 PM
Subject: IRB Notice

To: David Diaz Sanchez
Environmental Protection Agency
7315

From: Biomedical IRB

Approval Date: 10/28/2011
Expiration Date of Approval: 8/20/2012

RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)
Submission Type: Modification
Expedited Category: Minor Change to Previously Approved Research
Study #: 09-1625
Study Title: Epigenetic Effects of Diesel Exhaust and Ozone Exposure
Sponsors: US Environmental Protection Agency - GRANTS

This submission has been approved by the above IRB for the period indicated. It has been determined that the risk involved in this modification is no more than minimal. Unless otherwise noted, regulatory and other findings made previously for this study continue to be applicable.

Submission Description:
This amendment received 10/25/11 addresses the submission of a study reminder about the 1 hour post exposure bronchoscopies.

Investigator's Responsibilities:
Enclosed are stamped copies of approved consent documents and other recruitment materials (when applicable). You must copy the stamped consent forms for use with subjects unless you have approval to do otherwise.
This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR

50 & 56 (FDA), and 40 CFR 26 (EPA), where applicable.

CC: Michael Schmitt, Epa; Kelly Duncan, Kelly Duncan, Enviro Med Asthma And Lung Bio; Deepika Polineni, (EPA), Non-IRB Review Contact

IRB Informational Message—please do not use email REPLY to this address

Fw: IRB Notice
Deepika Polineni to: Mike Schmitt 11/02/2012 03:59 PM

From: Deepika Polineni/RTP/USEPA/US
To: Mike Schmitt/RTP/USEPA/US@EPA

---- Forwarded by Deepika Polineni/RTP/USEPA/US on 11/02/2012 03:59 PM ----

From: IRB <irb_no_reply@mailserv.grad.unc.edu>
To: David Diaz-Sanchez/RTP/USEPA/US@EPA
Cc: mschmitt@email.unc.edu, keduncan@email.unc.edu, keduncan@email.unc.edu, Deepika Polineni/RTP/USEPA/US@EPA
Date: 10/26/2011 07:45 AM
Subject: IRB Notice

TO: David Diaz Sanchez
Environmental Protection Agency
7315

FROM: Biomedical IRB

DATE: 10/26/2011

RE: Notice of Receipt of Modification Submission on 10/25/2011
STUDY #: 09-1625

STUDY TITLE: Epigenetic Effects of Diesel Exhaust and Ozone Exposure

Your submission for the above-referenced study has been received by the Office of Human Research Ethics and will be reviewed by the appropriate IRB.

Please refer to the above study number when corresponding with our office about this study.

If this is an initial application and you disclosed any potential conflict of interest in "Part A.3" it must be resolved with the COI review committee before your study can be reviewed by the IRB. Further information can be obtained at http://coi.unc.edu or 919.843.9953.

All other questions about your submission should be directed to 919.966.3113.

CC:
Michael Schmitt, Epa
Kelly Duncan, Enviro Med Asthma And Lung Bio
Kelly Duncan, Enviro Med Asthma And Lung Bio
Deepika Polineni, (EPA), Non-IRB Review Contact

IRB Informational Message—please do not use email REPLY to this address

Fw: IRB Notice
Deepika Polineni to: Mike Schmitt 11/02/2012 03:51 PM

From: Deepika Polineni/RTP/USEPA/US
To: Mike Schmitt/RTP/USEPA/US@EPA

---- Forwarded by Deepika Polineni/RTP/USEPA/US on 11/02/2012 03:51 PM ----

From: IRB <irb_no_reply@mailserv.unc.edu>
To: David Diaz-Sanchez/RTP/USEPA/US@EPA
Cc: mschmitt@email.unc.edu, keduncan@email.unc.edu, keduncan@email.unc.edu, Deepika Polineni/RTP/USEPA/US@EPA
Date: 04/11/2012 07:12 AM
Subject: IRB Notice

TO: David Diaz Sanchez
Environmental Protection Agency
7315

FROM: Biomedical IRB

DATE: 4/11/2012

RE: Notice of Receipt of Modification Submission on 4/10/2012
STUDY #: 09-1625

STUDY TITLE: Epigenetic Effects of Diesel Exhaust and Ozone Exposure

Your submission for the above-referenced study has been received by the Office of Human Research Ethics and will be reviewed by the appropriate IRB.

Please refer to the above study number when corresponding with our office about this study.

If this is an initial application and you disclosed any potential conflict of interest in "Part A.3" it must be resolved with the COI review committee before your study can be reviewed by the IRB. Further information can be obtained at http://coi.unc.edu or 919.843.9953.

All other questions about your submission should be directed to 919.966.3113.

CC:
Michael Schmitt, Epa
Kelly Duncan, Enviro Med Asthma And Lung Bio
Kelly Duncan, Enviro Med Asthma And Lung Bio
Deepika Polineni, (EPA), Non-IRB Review Contact

IRB Informational Message—please do not use email REPLY to this address

Fw: IRB Notice
Deepika Polineni to: Mike Schmitt 11/02/2012 03:50 PM

From: Deepika Polineni/RTP/USEPA/US
To: Mike Schmitt/RTP/USEPA/US@EPA

—— Forwarded by Deepika Polineni/RTP/USEPA/US on 11/02/2012 03:48 PM ——

From: IRB <irb_no_reply@mailserv.unc.edu>
To: David Diaz-Sanchez/RTP/USEPA/US@EPA
Cc: mschmitt@email.unc.edu, keduncan@email.unc.edu, keduncan@email.unc.edu, Deepika Polineni/RTP/USEPA/US@EPA
Date: 04/11/2012 11:12 AM
Subject: IRB Notice

To: David Diaz Sanchez
Environmental Protection Agency
7315

From: Biomedical IRB

Approval Date: 4/11/2012
Expiration Date of Approval: 8/20/2012

RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)
Submission Type: Modification
Expedited Category: Minor Change to Previously Approved Research
Study #: 09-1625

Study Title: Epigenetic Effects of Diesel Exhaust and Ozone Exposure
Sponsors: US Environmental Protection Agency - GRANTS

This submission has been approved by the IRB for the period indicated. It has been determined that the risk involved in this modification is no more than minimal. Unless otherwise noted, regulatory and other findings made previously for this study continue to be applicable.

Submission Description:
This modification, dated April 10, 2012, adds Juliette Kahle, Ph.D. to study personnel.

Investigator's Responsibilities:
IF YOU SUBMITTED ON PAPER, enclosed are stamped copies of approved consent documents and other recruitment materials (when applicable). You must copy the stamped consent forms for use with subjects unless you have approval to do otherwise. **IF YOU SUBMITTED ONLINE,** your approved consent forms and other documents are available online at http://apps.research.unc.edu.

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40 CFR 26 (EPA), where applicable.

CC:
Michael Schmitt, Epa
Kelly Duncan, Enviro Med Asthma And Lung Bio
Kelly Duncan, Enviro Med Asthma And Lung Bio
Deepika Polineni, (EPA), Non-IRB Review Contact

IRB Informational Message—please do not use email REPLY to this address

THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
Medical School Building 52
Mason Farm Road
CB #7097
Chapel Hill, NC 27599-7097
(919) 966-3113
Web site: ohre.unc.edu
Federalwide Assurance (FWA) #4801

To: David Diaz Sanchez
Environmental Protection Agency
7315

From: Biomedical IRB

Approval Date: 7/24/2012
Expiration Date of Approval: 7/23/2013

RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)
Submission Type: Renewal
Expedited Category: 8(c) Continuing Review - Data Analysis Only
Study #: 09-1625

Study Title: Epigenetic Effects of Diesel Exhaust and Ozone Exposure
Sponsors: US Environmental Protection Agency - GRANTS

This submission has been approved by the IRB for the period indicated.

Study Description:

Purpose: The purpose of this protocol is to compare the genetic and epigenetic effects between diesel exhaust and ozone exposure in healthy individuals and in mid/moderate asthmatics. Participants: The PI will recruit up to 30 mild to moderate asthmatics and up to 30 healthy adults to participate in this study. Procedures (methods): Subjects will be exposed to clean air, to 300 ug/m3 of diesel exhaust for 2 hours and to 0.3 ppm of ozone for 2 hours with intermittent exercise in a controlled environment chamber. Primary endpoints will include spirometry and lung cell changes post-exposure. Secondary, endpoints will include analysis of soluble factors present in plasma and bronchial lavage and analysis of intracellular factors present in lung tissue obtained from a brush biopsy.

Submission Description:

With this renewal, 4 are added to this applicaton: Jaspers, Ph.D., Michelle Hernandez, MD, Rebecca Bauer, BS, and Shaun McCullough, Ph.D.
Regulatory and other findings:

Based on the information provided, the IRB has determined that HIPAA does not apply to this study.

Social security numbers (SSN) may be collected for this study for tax identification purposes. The subject is required to disclose his/her SSN in order to receive the incentive payment(s).

This research, which was originally approved by the Full Board, is being renewed by the IRB under

Expedited Review, Category 8c. The research has been closed to the accrual of new subjects and all subjects have completed intervention/interaction. Renewal is granted for data analysis only.

Investigator's Responsibilities:

Federal regulations require that all research be reviewed at least annually. It is the Principal Investigator's responsibility to submit for renewal and obtain approval before the expiration date. You may not continue any research activity beyond the expiration date without IRB approval. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.

Your approved consent forms and other documents are available online at http://apps.research.unc.edu/irb/eform_routing.cfm?masterid=110492&Section=attachments

You are required to obtain IRB approval for any changes to any aspect of this study before they can be implemented. Any unanticipated problem involving risks to subjects or others (including adverse events reportable under UNC-Chapel Hill policy) should be reported to the IRB using the web portal at http://irbis.unc.edu.

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40CFR 26 (EPA), where applicable.

CC:
Michael Schmitt, Epa
Kelly Duncan, Enviro Med Asthma And Lung Bio
Kelly Duncan, Enviro Med Asthma And Lung Bio

Post Approval Submissions

Renewal Action Requested

ALERT: Modifications proposed as part of this renewal must be accomplished by editing the individual answers to the questions and data elements that make up the application. The modifications cannot be processed until the actual changes have been made throughout the application.

1.Renewal action requested by Principal Investigator (choose only one):

- ✗ This study involves direct interaction or intervention with subjects. Continue as approved.
- ✗ Enrollment of new subjects closed; interaction/intervention with previously enrolled subjects continues.
- ✗ Direct interaction with subjects completed but subsequent monitoring or follow up continues.
- ✓ Study involves DATA ANALYSIS ONLY. This includes (A) Studies that have always been limited to collection and analysis of existing data or specimens, OR (B) Studies that previously involved direct interaction or intervention with subjects that is now complete, including all contact and follow-up.

Please be aware that selecting Data Analysis Only will change the remainder of the application in ways that cannot be undone later. You should not click 'save and continue' if this is not a PERMANENT change in the study. Consult with the IRB if questions.

Progress Report

1.Number of Subjects involved through direct contact or use of their data (for multi-site studies, include only subjects covered by this IRB) (Note: **b+d** should not be larger than **a**)

A. Total projected number as approved by IRB:	80
B. Total number of subjects included/enrolled to date (do NOT include 'screen failures')	42
C. Number of subjects included/enrolled since last renewal:	13
D. Number to be included/enrolled in upcoming year	0

2.Have any subjects withdrawn voluntarily or been withdrawn from the study?

Yes

If yes, explain; give number and reasons for withdrawals.

We had a total of 4 subjects that either voluntarily withdrew or were withdrawn by the investigator since the last renewal. 1 subject was excluded based on frequent cancellations and never called back to reschedule. 1 subject was excluded by the investigator due to elevated resting heart rates during the expsoure. 1 subject opted out of the Bronchoscopy which excluded them from the study. And 1 subject was excluded by the investigator based on post exposure lung fuction values that exceeded our inclusion criterion for lung function.

3.Have there been any complaints about the research from subjects or others?

No

4.Have there been any findings (e.g., publications, new information, study results) that alter the risk/benefit ratio or otherwise impact the study?

No

5.Have there been any relevant multi-site reports?

No

6.Does this study have a Data and Safety Monitoring Committee (DSMC or DSMB)?

No

7.Have there been any deviations since the last renewal?

No

8.Have there been any unanticipated problems (including but not limited to adverse events and adverse subject outcomes) since the last renewal?

No

9.Are you requesting any modifications to the study, the consent documents, or any related documents at the time of this renewal?

Yes

Any modifications requested as part of this renewal should be incorporated into the application at this time. This includes uploading any revised attachments. Consent forms should be revised within the 'Consent Forms' section of this application. Please provide a brief summary of your requested modifications in the box below. Clearly distinguish new and revised attachments and consent forms from those previously approved.

If you are entering this study online for the first time (e.g., converting your existing paper-based application), please provide adequate details below for the IRB reviewers to identify your changes, including the section(s) where they will occur. Failure to do so will make it difficult for the IRB reviewers to find the changes and will delay your review.

I have include a copy of the front page of the "hardcopy" IRB application showing the addition of 4 investigators to the first page of the existining paper-based applicaton. The 4 investigators are Ilona Jaspers, Ph.D., Michelle Hernandez, MD, Rebecca Bauer, BS, and Shaun McCullough, Ph.D. I have dated this "new" front page of the existing paper-based application as July 23, 2012.

Office of Human Research Ethics

Institutional Review Board

Application for IRB Approval of
Human Subjects Research

Version June 25, 2009

Part A.1. Contact Information, Agreements, and Signatures

Date: July 23, 2012

IRB Study #09-1625

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

Name and degrees of Principal Investigator: David Diaz-Sanchez, Ph.D.; Kelly Duncan, Ph.D.

Department: US EPA Mailing address/CB #: 104 Mason Farm Road

Chapel Hill, NC 27514

UNC-CH PID: 714339670 Pager:

Phone #: 919-966-0676 Fax #: 919-966-6271

Email Address: Diaz-Sanchez.David@epa.gov, Duncan.kelly@epa.gov

For trainee-led projects: __ undergraduate __ graduate __ postdoc __ resident __ other

Name of faculty advisor:

Department: Mailing address/CB #:

Phone #: Fax #: Email Address:

Center, institute, or department in which research is based if other than department(s) listed above:

Name of Project Manager or Study Coordinator (if any): Michael Schmitt, MSPH

Department: US EPA Mailing address/CB #: 104 Mason Farm Road

Chapel Hill, NC 27514

Phone #: 919-966-0647 Fax #: 919-966-6271 Email Address: Schmitt.mike@epa.gov

List **all other project personnel** including co-investigators, and anyone else who has contact with subjects or identifiable data from subjects. **Include name, location (UNC or specific outside location), role and email address for each person who should receive electronic copies of IRB correspondence to PI.**

Robert Devlin, PhD.; Heidi Hiers, RN; Maryann Bassett, RN; Martin Case, BS; Andrew Ghio MD; Martha Sue Carraway, MD; Robert Truckner, MD;Howard Kehrl, MD; Tracey Montilla, RN; Michael Schmitt, MSPH, Sarah Snyder, B.S.; Melanie J. Jardim, Ph.D, Kristen Sanders, B.S., Juliette Kahle, Ph.D., Ilona Jaspers, Ph.D., Michelle Hernandez, MD, Rebecca Bauer, BS, Shaun McCullough, Ph.D.

Do any of the proposed changes increase risk?

No

10. Has this study been audited by a sponsor or monitor since approved or last renewed?

No

11. Will you be obtaining consent (initial or re-consent) from subjects in the upcoming approval period?

No

Reminder: If applicable, be sure to delete any consent forms that will no longer be used for your study. Consent forms are accessed via the navigation panel to the left under the "Consent Forms" section.

Data Analysis

You have indicated that your study now involves data analysis only.

- *Therefore, you are being presented with an abbreviated version of the application that contains*

limited information only. All questions are worded in future tense for new applications; you should answer them in the past tense because your research has already occurred.

- *You will not be allowed to make modifications or updates to the rest of the application.*
- *It is expected that the study will be limited to analysis of data obtained under the previously approved protocol.*

If this is incorrect, click the "Delete Submission" button on the bottom left and start the renewal process over.

General Information

1. General Information

1.Project Title

Epigenetic Effects of Diesel Exhaust and Ozone Exposure

2.**Brief Summary**. Provide a brief non-technical description of the study, which will be used in IRB documentation as a description of the study. Typical summaries are 50-100 words. Please reply to each item below, retaining the subheading labels already in place, so that reviewers can readily identify the content. PLEASE NOTE: THIS SECTION MAY BE EDITED BY THE IRB FOR CLARITY OR LENGTH.

Purpose: The purpose of this protocol is to compare the genetic and epigenetic effects between diesel exhaust and ozone exposure in healthy individuals and in mid/moderate asthmatics. Participants: The PI will recruit up to 30 mild to moderate asthmatics and up to 30 healthy adults to participate in this study. Procedures (methods): Subjects will be exposed to clean air, to 300 ug/m3 of diesel exhaust for 2 hours and to 0.3 ppm of ozone for 2 hours with intermittent exercise in a controlled environment chamber. Primary endpoints will include spirometry and lung cell changes post-exposure. Secondary, endpoints will include analysis of soluble factors present in plasma and bronchial lavage and analysis of intracellular factors present in lung tissue obtained from a brush biopsy.

2. Project Personnel

1.Will this project be led by a STUDENT (undergraduate, graduate) or TRAINEE (resident, fellow, postdoc), working in fulfillment of requirements for a University course, program or fellowship?

No

2.List all project personnel beginning with principal investigator, followed by faculty advisor, co-investigators, study coordinators, and anyone else who has contact with subjects or identifiable data from subjects.

- List ONLY those personnel for whom this IRB will be responsible; do NOT include collaborators who will remain under the oversight of another IRB **for this study**.
- If this is Community Based Participatory Research (CBPR) or you are otherwise working with community partners (who are not functioning as researchers), you may not be required to list them here as project personnel; consult with your IRB.
- If your extended research team includes multiple individuals with limited roles, you may not be required to list them here as project personnel; consult with your IRB.

The table below will access campus directory information; if you do not find your name, your directory listing may need to be updated.

Last Name	First Name	Department Name	Role	Detail
Sanchez	David Diaz	Environmental Protection Agency	Principal Investigator	view
Schmitt	Michael	Epa	Project Manager or Study Coordinator	view
Devlin	Robert	Pediatrics	Co-investigator	view

Bassett	Mary	Epa	Staff	view
Case	Martin	Epa	Co-Investigator	view
Ghio	Andrew	Medicine	Co-investigator	view
Carraway	Martha Sue		Co-Investigator	view
Kehrl	Howard	Medicine	Co-investigator	view
Montilla	Tracey		Staff	view
Truckner	Robert	Environment Sciences And Engi	Other (Read Only Access)	view
Duncan	Kelly	Enviro Med Asthma And Lung Bio	Co-Investigator	view
Snyder	Sarah	Epa	Other (Read Only Access)	view
Duncan	Kelly	Enviro Med Asthma And Lung Bio	Co-Investigator	view
Sanders	Kristen	Epa	Other (Read Only Access)	view
Kahle	Juliette	Environmental Protection Agency (epa)	Other (Read Only Access)	view
Jaspers	Ilona	Pediatrics	Other (Read Only Access)	view
Hernandez	Michelle	Pediatrics	Other (Read Only Access)	view
Bauer	Rebecca	Toxicology Curriculum	Other (Read Only Access)	view
McCullough	Shaun	Environmental Protection Agency (EPA)	Other (Read Only Access)	view

NOTE: The IRB database will link automatically to UNC Human Research Ethics Training database and the UNC Conflict of Interest (COI) database. Once the study is certified by the PI, all personnel listed (for whom we have email addresses) will receive separate instructions about COI disclosures. The IRB will communicate with the personnel listed above or the PI if further documentation is required.

3.If this research is based in a center, institute, or department (Administering Department) other than the one listed above for the PI, select here. Be aware that if you do not enter anything here, the PI's home department will be AUTOMATICALLY inserted when you save this page.

Department	Environmental Protection Agency

3. Funding Sources

1.Is this project funded (or proposed to be funded) by a contract or grant from an organization external to UNC-Chapel Hill?

Yes

Funding Source(s) or Sponsor(s)

Sponsor Name	UNC Ramses Number	Sponsor Type	Prime Sponsor Name	Prime Sponsor Type	Sponsor/Grant Number	Detail
US Environmental Protection Agency - GRANTS						view

2.Is this study funded by UNC-CH (e.g., department funds, internal pilot grants, trust accounts)?

No

3.Is this research classified (e.g. requires governmental security clearance)?

No

4.Is there a master protocol, grant application, or other proposal supporting this submission (check all that apply)?

- ✖ Grant Application
- ✖ Industry Sponsor Master Protocol
- ✖ Student Dissertation or Thesis Proposal
- ✖ Investigator Initiated Master Protocol
- ✖ Other Study Protocol

4. Screening Questions

1.Are any personnel, organizations, entities, facilities or locations in addition to UNC-Chapel Hill involved in this research (e.g., is this a multi-site study or does it otherwise involve locations outside UNC-CH, including foreign locations)?

No

By certifying below, the Principal Investigator affirms the following:

I will personally conduct or supervise this research study. I will ensure that this study is performed in compliance with all applicable laws, regulations and University policies regarding human subjects research. I will obtain IRB approval before making any changes or additions to the project. I will notify the IRB of any other changes in the information provided in this application. I will provide progress reports to the IRB at least annually, or as requested. I will report promptly to the IRB all unanticipated problems or serious adverse events involving risk to human subjects. I will follow the IRB approved consent process for all subjects. I will ensure that all collaborators, students and employees assisting in this research study are informed about these obligations. All information given in this form is accurate and complete.

If PI is a Student or Trainee Investigator, the Faculty Advisor also certifies the following:

I accept ultimate responsibility for ensuring that this study complies with all the obligations listed above for the PI.

Certifying Signatures:

Signature: Electronic Signature Received **Date:** 7/23/2012 03:09:41 PM
David Diaz Sanchez

THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
Medical School Building 52
Mason Farm Road
CB #7097
Chapel Hill, NC 27599-7097
(919) 966-3113
Web site: ohre.unc.edu
Federalwide Assurance (FWA) #4801

To: David Diaz Sanchez
Environmental Protection Agency

From: Biomedical IRB

Approval Date: 1/10/2013
Expiration Date of Approval: 7/23/2013

RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)
Submission Type: Modification
Expedited Category: Minor Change to Previously Approved Research
Study #: 09-1625

Study Title: Epigenetic Effects of Diesel Exhaust and Ozone Exposure
Sponsors: US Environmental Protection Agency - GRANTS

This submission has been approved by the IRB for the period indicated. It has been determined that the risk involved in this modification is no more than minimal. Unless otherwise noted, regulatory and other findings made previously for this study continue to be applicable.

Submission Description:

This is to notify the IRB that t he Office of the Inspector General of the Environmental Protection Agency (EPA) is performing an evaluation of EPA's human research. They have chosen several studies to audit. One of the studies is Epigenetic effects of diesel exhaust and ozone exposure (LAMARCK) IRB#09-1625, for which I am the Principal Investigator. As part of the audit they will be reviewing material with Personally Identifiable Information (PII) including consent forms and participants' name and contact information. They may also contact a small number of participants to determine their experience in the studies. The initial contact with these participants to determine their willingness to assist with this process will be via the Principal Investigator. Thank you, and please let me know if I can provide any further information.

Investigator's Responsibilities:
Your approved consent forms and other documents are available online at http://apps.research.unc.edu/irb/irb_event.cfm?actn=info&irbid=09-1625.

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40 CFR 26 (EPA), where applicable.

CC:
Michael Schmitt, Epa
Kelly Duncan, Enviro Med Asthma And Lung Bio

THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
Medical School Building 52
Mason Farm Road
CB #7097
Chapel Hill, NC 27599-7097
(919) 966-3113
Web site: ohre.unc.edu
Federalwide Assurance (FWA) #4801

The documents listed below are included with the IRB approval dated 01/10/2013 for study number 09-1625 entitled "Epigenetic Effects of Diesel Exhaust and Ozone Exposure":

File Name	Document Type
IRB submitted_suggested language for LETTER contact by PI_2013_Lamarck.docx	Other
Information Request for the OIG EPA Human Subjects Research Ass-1.pdf	Other
Memo to ORD NHEERL Principal Investigator David Diaz-Sanchez re- Human Subjects Research Information Request--12-10-12.pdf	Other
Memo to ORD re- Human Subjects Research Information Request--11-29-12-2.pdf	Other
Notification Memo-ORD Human Subjects Research--10-22-12-2.doc	Other
igactasof1010.pdf	Other

Information Request for the OIG EPA Human Subjects Research Assignment

Renee McGhee-Lenart to: Hyon Kim 11/05/2012 05:09 PM

Cc: Deborah Heckman, Norman Adkins

History: This message has been forwarded.

Hyon,

We request the following information for the OIG's EPA Human Subjects Research Assignment. We would like to receive this information as soon as possible and before the entrance conference. Please send any electronic files to Rick Beusse and myself. For hard copy information, we have team members in Washington DC and RTP. We could have Julie Narimatsu pick up information in Washington D.C. and Chris Dunlap pick up information at RTP.

Please let me know if you have any questions.

Thank you for your assistance.

Renee

Information Requested Ahead of the Entrance Conference

1. Program budgets and resource allocations for offices conducting controlled exposure human studies. (FY 2010, FY 2011, and FY 2012)
2. EPA's human study research policies, procedures, guidance, and protocols (we have the following):
   a. 40 CFR 26
   b. EPA Order 1000.17 Change A1.
   c. NHEERL Human Research Guidance, June 2009
   d. University of North Carolina at Chapel Hill, Human Research Protection Program, Standard Operating Procedures, June 21, 2012
3. The XCON, OMEGACON, KINGCON, and any related studies' protocol packages approved by the IRB and HSRRO from the beginning of the studies to the present including any amendments and/or modifications.
4. Any other paperwork submitted to IRB and HSRRO for approval of, clarification of, or explanation of the XCON, OMEGACON, KINGCON, and any related studies from the beginning of the studies to the present including any amendments and/or modifications.
5. Documentation of the process and decisions (i.e.,. studies, models, or other information) EPA used in deciding what level(s) of PM/diesel exhaust the 41 human subjects would be exposed to and the length of time of exposure.
6. All IRB minutes discussing the studies.
7. All HSRB minutes discussing the studies.
8. Recruiting materials for the XCON, OMEGACON, KINGCON, and any related studies from the beginning of the studies to the present (i.e., internet ads / announcements, newspaper ads /announcement, hard copy flyers, bulletin board postings, etc.)
9. Consent forms for the 41 human subjects who participated in the XCON, OMEGACON, KINGCON, and any related studies that exposed human subjects to concentrated airborne

particles or diesel exhaust emissions from 2010 to 2011

10. Documentation of all oral explanations given to the human subjects of the XCON, OMEGACON, KINGCON, and any related studies that exposed human subjects to concentrated airborne particles or diesel exhaust emissions from 2010 to 2011.
11. All correspondence between the IRB and the studies' investigators pertaining to any adverse or unexpected events or unanticipated problems related to the XCON, KINGCON, OMEGACON and any related studies from 2010-2011.
12. A list of the human exposure studies EPA has conducted over the last 7 years involving exposure to PM or diesel exhaust and the number of human subjects who participated in the studies. (documentation listing studies and dates the studies were done)
13. Name and contact information for the following individuals:
    a. Principal Investigators for XCON, KINGCON, OMEGACON, and any related studies
    b. IRB Board Members that approved the XCON, KINGCON, OMEGACON, and any related studies
    c. Dosing Review Officers for the XCON, KINGCON, OMEGCON, and any related studies
    d. 41 human subjects that participated in XCON, KINGCON, and OMEGACON human exposure studies for PM and/or diesel exhaust emissions from 2010 to 2011.

Renee McGhee-Lenart
Assignment Manager
EPA's Office of Inspector General
11201 Renner Boulevard
Lenexa, KS 66219
(913) 551-7534

This is to notify the IRB that the Office of the Inspector General of the Environmental Protection Agency (EPA) is performing an evaluation of EPA's human research. They have chosen several studies to audit. One of the studies is "Physiological changes in adults with metabolic syndrome exposed to concentrated ultrafine Chapel Hill air particles" (XCON), IRB#04-1677 (formerly GCRC #2067), for which I am the Principal Investigator. As part of the audit they will be reviewing material with Personally Identifiable Information (PII) including consent forms and participants' name and contact information. They may also contact a small number of participants to determine their experience in the studies. The initial contact with these participants to determine their willingness to assist with this process will be via the Principal Investigator. Thank you, and please let me know if I can provide any further information.

This is to notify the IRB that the Office of the Inspector General of the Environmental Protection Agency (EPA) is performing an evaluation of EPA's human research. They have chosen several studies to audit. One of the studies is "Mechanisms by which air pollution particles exacerbate asthma in older adults with mild asthma" (KINGCON), IRB#06-0548, for which I am the Principal Investigator. As part of the audit they will be reviewing material with Personally Identifiable Information (PII) including consent forms and participants' name and contact information. They may also contact a small number of participants to determine their experience in the studies. The initial contact with these participants to determine their willingness to assist with this process will be via the Principal Investigator. Thank you, and please let me know if I can provide any further information.

This is to notify the IRB that the Office of the Inspector General of the Environmental Protection Agency (EPA) is performing an evaluation of EPA's human research. They have chosen several studies to audit. One of the studies is "Epigenetic effects of diesel exhaust and ozone exposure" (LAMARCK) IRB#09-1625, for which I am the Principal Investigator. As part of the audit they will be reviewing material with Personally Identifiable Information (PII) including consent forms and participants' name and contact information. They may also contact a small number of participants to determine their experience in the studies. The initial contact with these participants to determine their willingness to assist with this process will be via the Principal Investigator. Thank you, and please let me know if I can provide any further information.

This is to notify the IRB that the Office of the Inspector General of the Environmental Protection Agency (EPA) is performing an evaluation of EPA's human research. They have chosen several studies to audit. One of the studies is "Cardiopulmonary Responses to Exposure to Ozone and Diesel Exhaust with Moderate Exercise in Healthy Young Adults" (DEPOZ) IRB#09-1344, for which I am the Principal Investigator. As part of the audit they will be reviewing material with Personally Identifiable Information (PII) including consent forms and participants' name and contact information. They may also contact a small number of participants to determine their experience in the studies. The initial contact with these participants to determine their willingness to assist with this process will be via the Principal Investigator. Thank you, and please let me know if I can provide any further information.

This is to notify the IRB that the Office of the Inspector General of the Environmental Protection Agency (EPA) is performing an evaluation of EPA's human research. They have chosen several studies to audit. One of the studies is "Title xxxxxxxxxxxxxxx Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx"(OMEGACON) IRB#07-0190, for which I am the Principal Investigator. As part of the audit they will be reviewing material with Personally Identifiable Information (PII) including consent forms and participants' name and contact information. They may also contact a small number of participants to determine their experience in the studies. The initial contact with these participants to determine their willingness to assist with this process will be via the Principal Investigator. Thank you, and please let me know if I can provide any further information.

THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
Medical School Building 52
Mason Farm Road
CB #7097
Chapel Hill, NC 27599-7097
(919) 966-3113
Web site: ohre.unc.edu
Federalwide Assurance (FWA) #4801

To: David Diaz Sanchez
Environmental Protection Agency

From: Biomedical IRB

Date: 12/20/2012 **RE**: Contingencies to be addressed following IRB Review
Submission Type: Modification
Study #: 09-1625

Study Title: Epigenetic Effects of Diesel Exhaust and Ozone Exposure

This submission has been reviewed by the IRB. This is not an IRB approval. You may not implement the research activities described in your submission until you have received a memo indicating final IRB approval. The IRB determined that this submission MAY BE APPROVED, pending stipulated change(s) and/or clarification(s).

Your review will be found online at the link below. You will be able to respond to each stipulation using the online system.
http://apps.research.unc.edu/irb/eform_routing.cfm?masterid=116660&Section=attachments

CC:
Michael Schmitt, Epa
Kelly Duncan, Enviro Med Asthma And Lung Bio

Number of Stipulations: 1

Post Approval Submissions

Modification Information

Provide a brief non-technical summary of any changes you will be making to the study. The text you enter here will be reproduced in the IRB approval document, and should contain the details that you and/or your sponsor find relevant (e.g., master protocol/amendment version number and date). Typical summaries are 50-100 words. Include a list of any documents that have been modified or added. PLEASE NOTE: THIS SECTION MAY BE EDITED BY THE IRB FOR CLARITY OR LENGTH.

For IRB documentation purposes, please upload a copy of the information that will be mailed or verbally conveyed to subjects by the PI.

Post Approval Submissions

Modification Information

ALERT: During the transition to online IRB applications, we are offering the following choices as a convenience between now and your next renewal. THIS APPLIES TO MODIFICATIONS ONLY.

If the application for this study was created ONLINE, you should proceed as directed below.

If the application for this study is currently on PAPER, you have two options to submit a modification:
1) You can continue to submit on paper until your next renewal is due. You may access the paper-based modification form here.
2) You can proceed with your online modification as directed below. This requires the conversion of your full application to the online format. Basic information about your study from the existing IRB database has been carried forward; however, the majority of information from your paper application will need to be entered at this time.

To modify an approved study, edit the individual answers that make up the application. The questions below are intended solely for the IRB to have a summary statement of your requested action. The modifications cannot be processed until the actual changes have been made throughout the application.

1.Provide a brief non-technical summary of any changes you will be making to the study. The text you enter here will be reproduced in the IRB approval document, and should contain the details that you and/or your sponsor find relevant (e.g., master protocol/amendment version number and date). Typical summaries are 50-100 words. Include a list of any documents that have been modified or added. PLEASE NOTE: THIS SECTION MAY BE EDITED BY THE IRB FOR CLARITY OR LENGTH.

This is to notify the IRB that t he Office of the Inspector General of the Environmental Protection Agency (EPA) is performing an evaluation of EPA's human research. They have chosen several studies to audit. One of the studies is Epigenetic effects of diesel exhaust and ozone exposure (LAMARCK) IRB#09-1625, for which I am the Principal Investigator. As part of the audit they will be reviewing material with Personally Identifiable Information (PII) including consent forms and participants' name and contact information. They may also contact a small number of participants to determine their experience in the studies. The initial contact with these participants to determine their willingness to assist with this process will be via the Principal Investigator. Thank you, and please let me know if I can provide any further information.

2.Is this modification being submitted in response to an unanticipated problem/adverse event or new findings?

No

3.Do any of the proposed changes increase risk?

No

4.Does this modification involve new information that requires reconsent of CURRENT subjects?

No

5.Is this study permanently closed to enrollment of subjects, all interventions and follow-up complete, and open for DATA ANALYSIS ONLY?

Yes

Please be aware that answering "Yes" to this question will change the remainder of the application in ways that cannot be undone later. You should not click "save and continue" if this is not a PERMANENT change in the study. Consult with the IRB if questions.

Data Analysis

You have indicated that your study now involves data analysis only.

- *Therefore, you are being presented with an abbreviated version of the application that contains limited*

information only. All questions are worded in future tense for new applications; you should answer them in the past tense because your research has already occurred.

- *You will not be allowed to make modifications or updates to the rest of the application.*
- *It is expected that the study will be limited to analysis of data obtained under the previously approved protocol.*

If this is incorrect, click the "Delete Submission" button on the bottom left and start the renewal process over.

General Information

1. General Information

1.Project Title

Epigenetic Effects of Diesel Exhaust and Ozone Exposure

2.**Brief Summary**. Provide a brief non-technical description of the study, which will be used in IRB documentation as a description of the study. Typical summaries are 50-100 words. Please reply to each item below, retaining the subheading labels already in place, so that reviewers can readily identify the content. PLEASE NOTE: THIS SECTION MAY BE EDITED BY THE IRB FOR CLARITY OR LENGTH.

Purpose: The purpose of this protocol is to compare the genetic and epigenetic effects between diesel exhaust and ozone exposure in healthy individuals and in mid/moderate asthmatics. Participants: The PI will recruit up to 30 mild to moderate asthmatics and up to 30 healthy adults to participate in this study. Procedures (methods): Subjects will be exposed to clean air, to 300 ug/m3 of diesel exhaust for 2 hours and to 0.3 ppm of ozone for 2 hours with intermittent exercise in a controlled environment chamber. Primary endpoints will include spirometry and lung cell changes post-exposure. Secondary, endpoints will include analysis of soluble factors present in plasma and bronchial lavage and analysis of intracellular factors present in lung tissue obtained from a brush biopsy.

2. Project Personnel

1.Will this project be led by a STUDENT (undergraduate, graduate) or TRAINEE (resident, fellow, postdoc), working in fulfillment of requirements for a University course, program or fellowship?

No

2.List all project personnel beginning with principal investigator, followed by faculty advisor, co-investigators, study coordinators, and anyone else who has contact with subjects or identifiable data from subjects.

- List ONLY those personnel for whom this IRB will be responsible; do NOT include collaborators who will remain under the oversight of another IRB **for this study**.
- If this is Community Based Participatory Research (CBPR) or you are otherwise working with community partners (who are not functioning as researchers), you may not be required to list them here as project personnel; consult with your IRB.
- If your extended research team includes multiple individuals with limited roles, you may not be required to list them here as project personnel; consult with your IRB.

The table below will access campus directory information; if you do not find your name, your directory listing may need to be updated.

Last Name	First Name	Department Name	Role	Detail
Sanchez	David Diaz	Environmental Protection Agency	Principal Investigator	view
Schmitt	Michael	Epa	Project Manager or Study Coordinator	view
Devlin	Robert	Pediatrics	Co-investigator	view
Bassett	Mary	Epa	Staff	view

Case	Martin	Epa	Co-Investigator	view
Ghio	Andrew	Medicine	Co-investigator	view
Carraway	Martha Sue		Co-Investigator	view
Kehrl	Howard	Medicine	Co-investigator	view
Montilla	Tracey		Staff	view
Duncan	Kelly	Enviro Med Asthma And Lung Bio	Co-Investigator	view
Kahle	Juliette	Environmental Protection Agency (epa)	Other (Read Only Access)	view
Jaspers	Ilona	Pediatrics	Other (Read Only Access)	view
Hernandez	Michelle	Pediatrics	Other (Read Only Access)	view
Bauer	Rebecca	Toxicology Curriculum	Other (Read Only Access)	view
McCullough	Shaun	Environmental Protection Agency (EPA)	Other (Read Only Access)	view
				view

NOTE: The IRB database will link automatically to UNC Human Research Ethics Training database and the UNC Conflict of Interest (COI) database. Once the study is certified by the PI, all personnel listed (for whom we have email addresses) will receive separate instructions about COI disclosures. The IRB will communicate with the personnel listed above or the PI if further documentation is required.

3.If this research is based in a center, institute, or department (Administering Department) other than the one listed above for the PI, select here. Be aware that if you do not enter anything here, the PI's home department will be AUTOMATICALLY inserted when you save this page.

Department	Environmental Protection Agency

3. Funding Sources

1.Is this project funded (or proposed to be funded) by a contract or grant from an organization external to UNC-Chapel Hill?

Yes

Funding Source(s) or Sponsor(s)

Sponsor Name	UNC Ramses Number	Sponsor Type	Prime Sponsor Name	Prime Sponsor Type	Sponsor/Grant Number	Detail
US Environmental Protection Agency - GRANTS						view

2.Is this study funded by UNC-CH (e.g., department funds, internal pilot grants, trust accounts)?

No

3.Is this research classified (e.g. requires governmental security clearance)?

No

4.Is there a master protocol, grant application, or other proposal supporting this submission (check all that apply)?

- ✗ Grant Application
- ✗ Industry Sponsor Master Protocol
- ✗ Student Dissertation or Thesis Proposal
- ✗ Investigator Initiated Master Protocol
- ✗ Other Study Protocol

4. Screening Questions

1. Are any personnel, organizations, entities, facilities or locations in addition to UNC-Chapel Hill involved in this research (e.g., is this a multi-site study or does it otherwise involve locations outside UNC-CH, including foreign locations)?

   No

Part A. Questions Common to All Studies

A.9. Identifiers

1. Check all of the following identifiers you will be receiving. This does not apply to information on consent forms.

- ✓ Names
- ✓ Telephone numbers
- ✓ Any elements of dates (other than year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death. For ages over 89: all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 and older
- ✓ Any geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code and their equivalent geocodes (e.g. GPS coordinates), except for the initial three digits of a zip code
- ✗ Fax numbers
- ✓ Electronic mail addresses
- ✗ Social security numbers
- ✗ Medical record numbers
- ✗ Health plan beneficiary numbers
- ✗ Account numbers
- ✗ Certificate/license numbers
- ✗ Vehicle identifiers and serial numbers (VIN), including license plate numbers
- ✗ Device identifiers and serial numbers (e.g., implanted medical device)
- ✗ Web universal resource locators (URLs)
- ✗ Internet protocol (IP) address numbers
- ✗ Biometric identifiers, including finger and voice prints
- ✗ Full face photographic images and any comparable images

✘ Any other unique identifying number, code, or characteristic, other than dummy identifiers that are not derived from actual identifiers and for which the re-identification key is maintained by the health care provider and not disclosed to the researcher

2.For any identifiers checked, how will these identifiers be stored in relationship to the research data?

✘ with the research data (i.e., in the same data set and/or physical location)

✔ separate from the research data (i.e., coded with a linkage file stored in a different physical location)

3.Are you collecting Social Security Numbers to be used as a unique identifier for study tracking purposes for national registry or database? (Do not check yes if collecting SSN *only* for payment purposes; this will be addressed later.)

No

A.10. Confidentiality of the data

1.Will any of the groupings or subgroupings used in analysis be small enough to allow individuals to be identified?

No

Part C. Existing Data, Records, Specimens

C.1. Data Sources

1.What existing records, data or human biological specimens will you be using? (indicate all that apply): *

✘ Data already collected from another research study

Were the investigators for the current application involved in the original collection? --

✘ Patient specimens (tissues, blood, serum, surgical discards, etc.)

Has the clinical purpose for which they were collected been met before removal of any excess? --

✘ Data already collected for administrative purposes

✘ Medical records in any format, including paper or electronic. This would include MIMS, WebCIS, Carolina Data Warehouse (CDW).

Be aware that the medical record custodian may also require their own form, e.g., HD-974 if UNC-Health Care System. This link is provided as a courtesy and the form does not have to be submitted to the IRB.

✘ Data coming directly from a health plan, health care clearinghouse, or health care provider?

✘ Publicly available data

✘ Other

If you have checked any of the above items, provide a description of the data you propose to use, describing the type of data, how they were collected (including consent procedures), and where they currently reside.

--

2.Do the custodians of the data, records or specimens require a data use agreement?

No

Attachments

File Name	Document Type
IRB submitted_suggested language for LETTER contact by PI_2013_Lamarck.docx	Other
Information Request for the OIG EPA Human Subjects Research Ass-1.pdf	Other
Memo to ORD NHEERL Principal Investigator David Diaz-Sanchez re- Human Subjects Research Information Request--12-10-12.pdf	Other
Memo to ORD re- Human Subjects Research Information Request--11-29-12-2.pdf	Other
Notification Memo-ORD Human Subjects Research--10-22-12-2.doc	Other
igactasof1010.pdf	Other

view attachments

Addenda

Data Security Requirements

view addenda

By certifying below, the Principal Investigator affirms the following:

I will personally conduct or supervise this research study. I will ensure that this study is performed in compliance with all applicable laws, regulations and University policies regarding human subjects research. I will obtain IRB approval before making any changes or additions to the project. I will notify the IRB of any other changes in the information provided in this application. I will provide progress reports to the IRB at least annually, or as requested. I will report promptly to the IRB all unanticipated problems or serious adverse events involving risk to human subjects. I will follow the IRB approved consent process for all subjects. I will ensure that all collaborators, students and employees assisting in this research study are informed about these obligations. All information given in this form is accurate and complete.

This study proposes research that has been determined to include Security Level 2 data security requirements. I agree to accept responsibility for managing these risks appropriately in consultation with departmental and/or campus security personnel. The Data Security Requirements addendum can be reviewed here.

If PI is a Student or Trainee Investigator, the Faculty Advisor also certifies the following:

I accept ultimate responsibility for ensuring that this study complies with all the obligations listed above for the PI.

Certifying Signatures:

Signature: Electronic Signature Received **Date:** 12/19/2012 10:23:17 AM

David Diaz Sanchez

*** CURRENT THROUGH PUB. L. 111-259, ENACTED OCT. 7, 2010 ***

Inspector General Act of 1978, as amended

§ 1. Short title

This Act may be cited as the "Inspector General Act of 1978".

§ 2. Purpose and establishment of Offices of Inspector General; departments and agencies involved

In order to create independent and objective units--

(1) to conduct and supervise audits and investigations relating to the programs and operations of the establishments listed in section 12(2);

(2) to provide leadership and coordination and recommend policies for activities designed (A) to promote economy, efficiency, and effectiveness in the administration of, and (B) to prevent and detect fraud and abuse in, such programs and operations; and

(3) to provide a means for keeping the head of the establishment and the Congress fully and currently informed about problems and deficiencies relating to the administration of such programs and operations and the necessity for and progress of corrective action;

there is established--

(A) in each of such establishments an office of Inspector General, subject to subparagraph (B); and

(B) in the establishment of the Department of the Treasury--

(i) an Office of Inspector General of the Department of the Treasury; and

(ii) an Office of Treasury Inspector General for Tax Administration.

§ 3. Appointment of Inspector General; supervision; removal; political activities; appointment of Assistant Inspector General for Auditing and Assistant Inspector General for Investigations

(a) There shall be at the head of each Office an Inspector General who shall be appointed by the President, by and with the advice and consent of the Senate, without regard to political affiliation and solely on the basis of integrity and demonstrated ability in accounting, auditing, financial analysis, law, management analysis, public administration, or investigations. Each Inspector General shall report to and be under the general supervision of the head of the establishment involved or, to the extent such authority is delegated, the officer next in rank below such head, but shall not report to, or be subject to supervision by, any other officer of such establishment. Neither the head of the establishment nor the officer next in rank below such head shall prevent or prohibit the Inspector

General from initiating, carrying out, or completing any audit or investigation, or from issuing any subpena during the course of any audit or investigation.

(b) An Inspector General may be removed from office by the President. If an Inspector General is removed from office or is transferred to another position or location within an establishment, the President shall communicate in writing the reasons for any such removal or transfer to both Houses of Congress, not later than 30 days before the removal or transfer. Nothing in this subsection shall prohibit a personnel action otherwise authorized by law, other than transfer or removal.

(c) For the purposes of section 7324 of Title 5, United States Code, no Inspector General shall be considered to be an employee who determines policies to be pursued by the United States in the nationwide administration of Federal laws.

(d) Each Inspector General shall, in accordance with applicable laws and regulations governing the civil service--

(1) appoint an Assistant Inspector General for Auditing who shall have the responsibility for supervising the performance of auditing activities relating to programs and operations of the establishment, and

(2) appoint an Assistant Inspector General for Investigations who shall have the responsibility for supervising the performance of investigative activities relating to such programs and operations.

(e) The annual rate of basic pay for an Inspector General (as defined under section 12(3)) shall be the rate payable for level III of the Executive Schedule under section 5314 of title 5, United States Code, plus 3 percent.

(f) An Inspector General (as defined under section 8G(a)(6) or 12(3)) may not receive any cash award or cash bonus, including any cash award under chapter 45 of title 5, United States Code.

(g) Each Inspector General shall, in accordance with applicable laws and regulations governing the civil service, obtain legal advice from a counsel either reporting directly to the Inspector General or another Inspector General.

§ 4. Duties and responsibilities; report of criminal violations to Attorney General

(a) It shall be the duty and responsibility of each Inspector General, with respect to the establishment within which his Office is established--

(1) to provide policy direction for and to conduct, supervise, and coordinate audits and investigations relating to the programs and operations of such establishment;

(2) to review existing and proposed legislation and regulations relating to programs and operations of such establishment and to make recommendations in the semiannual reports required by section 5(a) concerning the impact of such legislation or regulations on the economy and efficiency in the administration of programs and operations administered or financed by such establishment or the prevention and detection of fraud and abuse in such programs and operations;

(3) to recommend policies for, and to conduct, supervise, or coordinate other activities carried out or financed by such establishment for the purpose of promoting economy and efficiency in the administration of, or preventing and detecting fraud and abuse in, its programs and operations;

(4) to recommend policies for, and to conduct, supervise, or coordinate relationships between such establishment

and other Federal agencies, State and local governmental agencies, and nongovernmental entities with respect to (A) all matters relating to the promotion of economy and efficiency in the administration of, or the prevention and detection of fraud and abuse in, programs and operations administered or financed by such establishment, or (B) the identification and prosecution of participants in such fraud or abuse; and

(5) to keep the head of such establishment and the Congress fully and currently informed, by means of the reports required by section 5 and otherwise, concerning fraud and other serious problems, abuses, and deficiencies relating to the administration of programs and operations administered or financed by such establishment, to recommend corrective action concerning such problems, abuses, and deficiencies, and to report on the progress made in implementing such corrective action.

(b)(1) In carrying out the responsibilities specified in subsection (a)(1), each Inspector General shall--

(A) comply with standards established by the Comptroller General of the United States for audits of Federal establishments, organizations, programs, activities, and functions;

(B) establish guidelines for determining when it shall be appropriate to use non-Federal auditors; and

(C) take appropriate steps to assure that any work performed by non-Federal auditors complies with the standards established by the Comptroller General as described in paragraph (1).

(2) For purposes of determining compliance with paragraph (1)(A) with respect to whether internal quality controls are in place and operating and whether established audit standards, policies, and procedures are being followed by Offices of Inspector General of establishments defined under section 12(2), Offices of Inspector General of designated Federal entities defined under section 8F(a)(2), and any audit office established within a Federal entity defined under section 8F(a)(1), reviews shall be performed exclusively by an audit entity in the Federal Government, including the Government Accountability Office or the Office of Inspector General of each establishment defined under section 12(2), or the Office of Inspector General of each designated Federal entity defined under section 8F(a)(2).

(c) In carrying out the duties and responsibilities established under this Act, each Inspector General shall give particular regard to the activities of the Comptroller General of the United States with a view toward avoiding duplication and insuring effective coordination and cooperation.

(d) In carrying out the duties and responsibilities established under this Act, each Inspector General shall report expeditiously to the Attorney General whenever the Inspector General has reasonable grounds to believe there has been a violation of Federal criminal law.

§ 5. Semiannual reports; transmittal to Congress; availability to public; immediate report on serious or flagrant problems; disclosure of information; definitions.

(a) Each Inspector General shall, not later than April 30 and October 31 of each year, prepare semiannual reports summarizing the activities of the Office during the immediately preceding six-month periods ending March 31 and September 30. Such reports shall include, but need not be limited to--

(1) a description of significant problems, abuses, and deficiencies relating to the administration of programs and operations of such establishment disclosed by such activities during the reporting period;

(2) a description of the recommendations for corrective action made by the Office during the reporting period with

respect to significant problems, abuses, or deficiencies identified pursuant to paragraph (1);

(3) an identification of each significant recommendation described in previous semiannual reports on which corrective action has not been completed;

(4) a summary of matters referred to prosecutive authorities and the prosecutions and convictions which have resulted;

(5) a summary of each report made to the head of the establishment under section 6(b)(2) during the reporting period;

(6) a listing, subdivided according to subject matter, of each audit report issued by the Office during the reporting period and for each report, where applicable, the total dollar value of questioned costs (including a separate category for the dollar value of unsupported costs) and the dollar value of recommendations that funds be put to better use;

(7) a summary of each particularly significant report;

(8) statistical tables showing the total number of audit reports, inspection reports, and evaluation reports and the total dollar value of questioned costs (including a separate category for the dollar value of unsupported costs), for reports--

(A) for which no management decision had been made by the commencement of the reporting period;

(B) which were issued during the reporting period;

(C) for which a management decision was made during the reporting period, including--

(i) the dollar value of disallowed costs; and

(ii) the dollar value of costs not disallowed; and

(D) for which no management decision has been made by the end of the reporting period;

(9) statistical tables showing the total number of audit reports, inspection reports, and evaluation reports and the dollar value of recommendations that funds be put to better use by management, for reports--

(A) for which no management decision had been made by the commencement of the reporting period;

(B) which were issued during the reporting period;

(C) for which a management decision was made during the reporting period, including--

(i) the dollar value of recommendations that were agreed to by management; and

(ii) the dollar value of recommendations that were not agreed to by management; and

(D) for which no management decision has been made by the end of the reporting period;

(10) a summary of each audit report issued before the commencement of the reporting period for which no management decision has been made by the end of the reporting period (including the date and title of each such report), an explanation of the reasons such management decision has not been made, and a statement concerning the desired timetable for achieving a management decision on each such report;

(11) a description and explanation of the reasons for any significant revised management decision made during the reporting period;

(12) information concerning any significant management decision with which the Inspector General is in disagreement;

(13) the information described under section 05(b) of the Federal Financial Management Improvement Act of 1996;

(14)(A) an appendix containing the results of any peer review conducted by another Office of Inspector General during the reporting period; or

(B) if no peer review was conducted within that reporting period, a statement identifying the date of the last peer review conducted by another Office of Inspector General;

(15) a list of any outstanding recommendations from any peer review conducted by another Office of Inspector General that have not been fully implemented, including a statement describing the status of the implementation and why implementation is not complete; and

(16) a list of any peer reviews conducted by the Inspector General of another Office of the Inspector General during the reporting period, including a list of any outstanding recommendations made from any previous peer review (including any peer review conducted before the reporting period) that remain outstanding or have not been fully implemented.

(b) Semiannual reports of each Inspector General shall be furnished to the head of the establishment involved not later than April 30 and October 31 of each year and shall be transmitted by such head to the appropriate committees or subcommittees of the Congress within thirty days after receipt of the report, together with a report by the head of the establishment containing--

(1) any comments such head determines appropriate;

(2) statistical tables showing the total number of audit reports, inspection reports, and evaluation reports and the dollar value of disallowed costs, for reports--

(A) for which final action had not been taken by the commencement of the reporting period;

(B) on which management decisions were made during the reporting period;

(C) for which final action was taken during the reporting period, including--

(i) the dollar value of disallowed costs that were recovered by management through collection, offset, property in lieu of cash, or otherwise; and

(ii) the dollar value of disallowed costs that were written off by management; and

(D) for which no final action has been taken by the end of the reporting period;

(3) statistical tables showing the total number of audit reports, inspection reports, and evaluation reports and the dollar value of recommendations that funds be put to better use by management agreed to in a management decision, for reports--

(A) for which final action had not been taken by the commencement of the reporting period;

(B) on which management decisions were made during the reporting period;

(C) for which final action was taken during the reporting period, including--

(i) the dollar value of recommendations that were actually completed; and

(ii) the dollar value of recommendations that management has subsequently concluded should not or could not be implemented or completed; and

(D) for which no final action has been taken by the end of the reporting period; and

(4) a statement with respect to audit reports on which management decisions have been made but final action has not been taken, other than audit reports on which a management decision was made within the preceding year, containing--

(A) a list of such audit reports and the date each such report was issued;

(B) the dollar value of disallowed costs for each report;

(C) the dollar value of recommendations that funds be put to better use agreed to by management for each report; and

(D) an explanation of the reasons final action has not been taken with respect to each such audit report, except that such statement may exclude such audit reports that are under formal administrative or judicial appeal or upon which management of an establishment has agreed to pursue a legislative solution, but shall identify the number of reports in each category so excluded.

(c) Within sixty days of the transmission of the semiannual reports of each Inspector General to the Congress, the head of each establishment shall make copies of such report available to the public upon request and at a reasonable cost. Within 60 days after the transmission of the semiannual reports of each establishment head to the Congress, the head of each establishment shall make copies of such report available to the public upon request and at a reasonable cost.

(d) Each Inspector General shall report immediately to the head of the establishment involved whenever the Inspector General becomes aware of particularly serious or flagrant problems, abuses, or deficiencies relating to the administration of programs and operations of such establishment. The head of the establishment shall transmit any such report to the appropriate committees or subcommittees of Congress within seven calendar days, together with a report by the head of the establishment containing any comments such head deems appropriate.

(e)(1) Nothing in this section shall be construed to authorize the public disclosure of information which is--

(A) specifically prohibited from disclosure by any other provision of law;

(B) specifically required by Executive order to be protected from disclosure in the interest of national defense or national security or in the conduct of foreign affairs; or

(C) a part of an ongoing criminal investigation.

(2) Notwithstanding paragraph (1)(C), any report under this section may be disclosed to the public in a form which includes information with respect to a part of an ongoing criminal investigation if such information has been included in a public record.

(3) Except to the extent and in the manner provided under section 6103(f) of the Internal Revenue Code of 1986 [26 U.S.C. § 6103(f)], nothing in this section or in any other provision of this Act shall be construed to authorize or permit the withholding of information from the Congress, or from any committee or subcommittee thereof.

(f) As used in this section--

(1) the term "questioned cost" means a cost that is questioned by the Office because of--

(A) an alleged violation of a provision of a law, regulation, contract, grant, cooperative agreement, or other agreement or document governing the expenditure of funds;

(B) a finding that, at the time of the audit, such cost is not supported by adequate documentation; or

(C) a finding that the expenditure of funds for the intended purpose is unnecessary or unreasonable;

(2) the term "unsupported cost" means a cost that is questioned by the Office because the Office found that, at the time of the audit, such cost is not supported by adequate documentation;

(3) the term "disallowed cost" means a questioned cost that management, in a management decision, has sustained or agreed should not be charged to the Government;

(4) the term "recommendation that funds be put to better use" means a recommendation by the Office that funds could be used more efficiently if management of an establishment took actions to implement and complete the recommendation, including--

(A) reductions in outlays;

(B) deobligation of funds from programs or operations;

(C) withdrawal of interest subsidy costs on loans or loan guarantees, insurance, or bonds;

(D) costs not incurred by implementing recommended improvements related to the operations of the establishment, a contractor or grantee;

(E) avoidance of unnecessary expenditures noted in preaward reviews of contract or grant agreements; or

(F) any other savings which are specifically identified;

(5) the term "management decision" means the evaluation by the management of an establishment of the findings and recommendations included in an audit report and the issuance of a final decision by management concerning its response to such findings and recommendations, including actions concluded to be necessary; and

(6) the term "final action" means--

(A) the completion of all actions that the management of an establishment has concluded, in its management decision, are necessary with respect to the findings and recommendations included in an audit report; and

(B) in the event that the management of an establishment concludes no action is necessary, final action occurs when a management decision has been made.

§ 6. Authority of Inspector General; information and assistance from Federal agencies; unreasonable refusal; office space and equipment

(a) In addition to the authority otherwise provided by this Act, each Inspector General, in carrying out the provisions of this Act, is authorized--

(1) to have access to all records, reports, audits, reviews, documents, papers, recommendations, or other material available to the applicable establishment which relate to programs and operations with respect to which that Inspector General has responsibilities under this Act;

(2) to make such investigations and reports relating to the administration of the programs and operations of the applicable establishment as are, in the judgment of the Inspector General, necessary or desirable;

(3) to request such information or assistance as may be necessary for carrying out the duties and responsibilities provided by this Act from any Federal, State, or local governmental agency or unit thereof;

(4) to require by subpoena the production of all information, documents, reports, answers, records, accounts, papers, and other data in any medium (including electronically stored information, as well as any tangible thing) and documentary evidence necessary in the performance of the functions assigned by this Act, which subpoena, in the case of contumacy or refusal to obey, shall be enforceable by order of any appropriate United States district court: *Provided,* That procedures other than subpenas shall be used by the Inspector General to obtain documents and information from Federal agencies;

(5) to administer to or take from any person an oath, affirmation, or affidavit, whenever necessary in the performance of the functions assigned by this Act, which oath, affirmation, or affidavit when administered or taken by or before an employee of an Office of Inspector General designated by the Inspector General shall have the same force and effect as if administered or taken by or before an officer having a seal;

(6) to have direct and prompt access to the head of the establishment involved when necessary for any purpose pertaining to the performance of functions and responsibilities under this Act;

(7) to select, appoint, and employ such officers and employees as may be necessary for carrying out the functions, powers, and duties of the Office subject to the provisions of Title 5, United States Code, governing appointments in the competitive service, and the provisions of chapter 51 and subchapter III of chapter 53 of such title relating

to classification and General Schedule pay rates;

(8) to obtain services as authorized by section 3109 of Title 5, United States Code, at daily rates not to exceed the equivalent rate prescribed for grade GS-18 of the General Schedule by section 5332 of Title 5, United States Code; and

(9) to the extent and in such amounts as may be provided in advance by appropriations Acts, to enter into contracts and other arrangements for audits, studies, analyses, and other services with public agencies and with private persons, and to make such payments as may be necessary to carry out the provisions of this Act.

(b)(1) Upon request of an Inspector General for information or assistance under subsection (a)(3), the head of any Federal agency involved shall, insofar as is practicable and not in contravention of any existing statutory restriction or regulation of the Federal agency from which the information is requested, furnish to such Inspector General, or to an authorized designee, such information or assistance.

(2) Whenever information or assistance requested under subsection (a)(1) or (a)(3) is, in the judgment of an Inspector General, unreasonably refused or not provided, the Inspector General shall report the circumstances to the head of the establishment involved without delay.

(c) Each head of an establishment shall provide the Office within such establishment with appropriate and adequate office space at central and field office locations of such establishment, together with such equipment, office supplies, and communications facilities and services as may be necessary for the operation of such offices, and shall provide necessary maintenance services for such offices and the equipment and facilities located therein.

(d)(1)(A) For purposes of applying the provisions of law identified in subparagraph (B)--

(i) each Office of Inspector General shall be considered to be a separate agency; and

(ii) the Inspector General who is the head of an office referred to in clause (i) shall, with respect to such office, have the functions, powers, and duties of an agency head or appointing authority under such provisions.

(B) This paragraph applies with respect to the following provisions of title 5, United States Code:

(i) Subchapter II of chapter 35.

(ii) Sections 8335(b), 8336, 8344, 8414, 8468, and 8425(b).

(iii) All provisions relating to the Senior Executive Service (as determined by the Office of Personnel Management), subject to paragraph (2).

(2) For purposes of applying section 4507(b) of title 5, United States Code, paragraph (1)(A)(ii) shall be applied by substituting "the Council of the Inspectors General on Integrity and Efficiency (established by section 11 of the Inspector General Act) shall" for "the Inspector General who is the head of an office referred to in clause (i) shall, with respect to such office,".

(e)(1) In addition to the authority otherwise provided by this Act, each Inspector General, any Assistant Inspector General for Investigations under such an Inspector General, and any special agent supervised by such an Assistant Inspector General may be authorized by the Attorney General to--

(A) carry a firearm while engaged in official duties as authorized under this Act or other statute, or as expressly authorized by the Attorney General;

(B) make an arrest without a warrant while engaged in official duties as authorized under this Act or other statute, or as expressly authorized by the Attorney General, for any offense against the United States committed in the presence of such Inspector General, Assistant Inspector General, or agent, or for any felony cognizable under the laws of the United States if such Inspector General, Assistant Inspector General, or agent has reasonable grounds to believe that the person to be arrested has committed or is committing such felony; and

(C) seek and execute warrants for arrest, search of a premises, or seizure of evidence issued under the authority of the United States upon probable cause to believe that a violation has been committed.

(2) The Attorney General may authorize exercise of the powers under this subsection only upon an initial determination that--

(A) the affected Office of Inspector General is significantly hampered in the performance of responsibilities established by this Act as a result of the lack of such powers;

(B) available assistance from other law enforcement agencies is insufficient to meet the need for such powers; and

(C) adequate internal safeguards and management procedures exist to ensure proper exercise of such powers.

(3) The Inspector General offices of the Department of Commerce, Department of Education, Department of Energy, Department of Health and Human Services, Department of Homeland Security, Department of Housing and Urban Development, Department of the Interior, Department of Justice, Department of Labor, Department of State, Department of Transportation, Department of the Treasury, Department of Veterans Affairs, Agency for International Development, Environmental Protection Agency, Federal Deposit Insurance Corporation, Federal Emergency Management Agency, General Services Administration, National Aeronautics and Space Administration, Nuclear Regulatory Commission, Office of Personnel Management, Railroad Retirement Board, Small Business Administration, Social Security Administration, and the Tennessee Valley Authority are exempt from the requirement of paragraph (2) of an initial determination of eligibility by the Attorney General.

(4) The Attorney General shall promulgate, and revise as appropriate, guidelines which shall govern the exercise of the law enforcement powers established under paragraph (1).

(5)(A) Powers authorized for an Office of Inspector General under paragraph (1) may be rescinded or suspended upon a determination by the Attorney General that any of the requirements under paragraph (2) is no longer satisfied or that the exercise of authorized powers by that Office of Inspector General has not complied with the guidelines promulgated by the Attorney General under paragraph (4).

(B) Powers authorized to be exercised by any individual under paragraph (1) may be rescinded or suspended with respect to that individual upon a determination by the Attorney General that such individual has not complied with guidelines promulgated by the Attorney General under paragraph (4).

(6) A determination by the Attorney General under paragraph (2) or (5) shall not be reviewable in or by any court.

(7) To ensure the proper exercise of the law enforcement powers authorized by this subsection, the Offices of Inspector General described under paragraph (3) shall, not later than 180 days after the date of enactment of this subsection, collectively enter into a memorandum of understanding to establish an external review process for

ensuring that adequate internal safeguards and management procedures continue to exist within each Office and within any Office that later receives an authorization under paragraph (2). The review process shall be established in consultation with the Attorney General, who shall be provided with a copy of the memorandum of understanding that establishes the review process. Under the review process, the exercise of the law enforcement powers by each Office of Inspector General shall be reviewed periodically by another Office of Inspector General or by a committee of Inspectors General. The results of each review shall be communicated in writing to the applicable Inspector General and to the Attorney General.

(8) No provision of this subsection shall limit the exercise of law enforcement powers established under any other statutory authority, including United States Marshals Service special deputation.

(9) In this subsection, the term "Inspector General" means an Inspector General appointed under section 3 or an Inspector General appointed under section 8G.

(f)(1) For each fiscal year, an Inspector General shall transmit a budget estimate and request to the head of the establishment or designated Federal entity to which the Inspector General reports. The budget request shall specify the aggregate amount of funds requested for such fiscal year for the operations of that Inspector General and shall specify the amount requested for all training needs, including a certification from the Inspector General that the amount requested satisfies all training requirements for the Inspector General's office for that fiscal year, and any resources necessary to support the Council of the Inspectors General on Integrity and Efficiency. Resources necessary to support the Council of the Inspectors General on Integrity and Efficiency shall be specifically identified and justified in the budget request.

(2) In transmitting a proposed budget to the President for approval, the head of each establishment or designated Federal entity shall include--

(A) an aggregate request for the Inspector General;

(B) amounts for Inspector General training;

(C) amounts for support of the Council of the Inspectors General on Integrity and Efficiency; and

(D) any comments of the affected Inspector General with respect to the proposal.

(3) The President shall include in each budget of the United States Government submitted to Congress--

(A) a separate statement of the budget estimate prepared in accordance with paragraph (1);

(B) the amount requested by the President for each Inspector General;

(C) the amount requested by the President for training of Inspectors General;

(D) the amount requested by the President for support for the Council of the Inspectors General on Integrity and Efficiency; and

(E) any comments of the affected Inspector General with respect to the proposal if the Inspector General concludes that the budget submitted by the President would substantially inhibit the Inspector General from performing the duties of the office.

§ 7. Complaints by employees; disclosure of identity; reprisals

(a) The Inspector General may receive and investigate complaints or information from an employee of the establishment concerning the possible existence of an activity constituting a violation of law, rules, or regulations, or mismanagement, gross waste of funds, abuse of authority or a substantial and specific danger to the public health and safety.

(b) The Inspector General shall not, after receipt of a complaint or information from an employee, disclose the identity of the employee without the consent of the employee, unless the Inspector General determines such disclosure is unavoidable during the course of the investigation.

(c) Any employee who has authority to take, direct others to take, recommend, or approve any personnel action, shall not, with respect to such authority, take or threaten to take any action against any employee as a reprisal for making a complaint or disclosing information to an Inspector General, unless the complaint was made or the information disclosed with the knowledge that it was false or with willful disregard for its truth or falsity.

§ 8. Additional provisions with respect to the Inspector General of the Department of Defense

(a) No member of the Armed Forces, active or reserve, shall be appointed Inspector General of the Department of Defense.

(b)(1) Notwithstanding the last two sentences of section 3(a), the Inspector General shall be under the authority, direction, and control of the Secretary of Defense with respect to audits or investigations, or the issuance of subpoenas, which require access to information concerning--

(A) sensitive operational plans;

(B) intelligence matters;

(C) counterintelligence matters;

(D) ongoing criminal investigations by other administrative units of the Department of Defense related to national security; or

(E) other matters the disclosure of which would constitute a serious threat to national security.

(2) With respect to the information described in paragraph (1) the Secretary of Defense may prohibit the Inspector General from initiating, carrying out, or completing any audit or investigation, or from issuing any subpoena, after the Inspector General has decided to initiate, carry out or complete such audit or investigation or to issue such subpoena, if the Secretary determines that such prohibition is necessary to preserve the national security interests of the United States.

(3) If the Secretary of Defense exercises any power under paragraph (1) or (2), the Inspector General shall submit a statement concerning such exercise within thirty days to the Committees on Armed Services and Governmental Affairs of the Senate and the Committee on Armed Services and the Committee on Government Reform and Oversight of the House of Representatives and to other appropriate committees or subcommittees of the Congress.

(4) The Secretary shall, within thirty days after submission of a statement under paragraph (3), transmit a statement of the reasons for the exercise of power under paragraph (1) or (2) to the congressional committees

specified in paragraph (3) and to other appropriate committees or subcommittees.

(c) In addition to the other duties and responsibilities specified in this Act, the Inspector General of the Department of Defense shall--

(1) be the principal adviser to the Secretary of Defense for matters relating to the prevention and detection of fraud, waste, and abuse in the programs and operations of the Department;

(2) initiate, conduct, and supervise such audits and investigations in the Department of Defense (including the military departments) as the Inspector General considers appropriate;

(3) provide policy direction for audits and investigations relating to fraud, waste, and abuse and program effectiveness;

(4) investigate fraud, waste, and abuse uncovered as a result of other contract and internal audits, as the Inspector General considers appropriate;

(5) develop policy, monitor and evaluate program performance, and provide guidance with respect to all Department activities relating to criminal investigation programs;

(6) monitor and evaluate the adherence of Department auditors to internal audit, contract audit, and internal review principles, policies, and procedures;

(7) develop policy, evaluate program performance, and monitor actions taken by all components of the Department in response to contract audits, internal audits, internal review reports, and audits conducted by the Comptroller General of the United States;

(8) request assistance as needed from other audit, inspection, and investigative units of the Department of Defense (including military departments); and

(9) give particular regard to the activities of the internal audit, inspection, and investigative units of the military departments with a view toward avoiding duplication and insuring effective coordination and cooperation.

(d) Notwithstanding section 4(d), the Inspector General of the Department of Defense shall expeditiously report suspected or alleged violations of chapter 47 of title 10, United States Code (Uniform Code of Military Justice), to the Secretary of the military department concerned or the Secretary of Defense.

(e) For the purposes of section 7, a member of the Armed Forces shall be deemed to be an employee of the Department of Defense, except that, when the Coast Guard operates as a service of another department or agency of the Federal Government, a member of the Coast Guard shall be deemed to be an employee of such department or agency.

(f)(1) Each semiannual report prepared by the Inspector General of the Department of Defense under section 5(a) shall include information concerning the numbers and types of contract audits conducted by the Department during the reporting period. Each such report shall be transmitted by the Secretary of Defense to the Committees on Armed Services and Governmental Affairs of the Senate and the Committee on Armed Services and the Committee on Government Reform and Oversight of the House of Representatives and to other appropriate committees or subcommittees of the Congress.

(2) Any report required to be transmitted by the Secretary of Defense to the appropriate committees or subcommittees of the Congress under section 5(d) shall also be transmitted, within the seven-day period specified in such section, to the congressional committees specified in paragraph (1).

(g) The provisions of section 1385 of title 18, United States Code, shall not apply to audits and investigations conducted by, under the direction of, or at the request of the Inspector General of the Department of Defense to carry out the purposes of this Act.

(h)(1) There is a General Counsel to the Inspector General of the Department of Defense, who shall be appointed by the Inspector General of the Department of Defense.

(2)(A) Notwithstanding section 140(b) of Title 10, the General Counsel is the chief legal officer of the Office of the Inspector General.

(B) The Inspector General is the exclusive legal client of the General Counsel.

(C) The General Counsel shall perform such functions as the Inspector General may prescribe.

(D) The General Counsel shall serve at the discretion of the Inspector General.

(3) There is an Office of the General Counsel to the Inspector General of the Department of Defense. The Inspector General may appoint to the Office to serve as staff of the General Counsel such legal counsel as the Inspector General considers appropriate.

(i)(1) The Inspector General of the Department of Defense is authorized to require by subpoena the attendance and testimony of witnesses as necessary in the performance of functions assigned to the Inspector General by this Act, except that the Inspector General shall use procedures other than subpoenas to obtain attendance and testimony from Federal employees.

(2) A subpoena issued under this subsection, in the case of contumacy or refusal to obey, shall be enforceable by order of any appropriate United States district court.

(3) The Inspector General shall notify the Attorney General 7 days before issuing any subpoena under this section.

§ 8A. Special provisions relating to the Agency for International Development

(a) In addition to the other duties and responsibilities specified in this Act, the Inspector General of the Agency for International Development shall supervise, direct, and control all security activities relating to the programs and operations of that Agency, subject to the supervision of the Administrator of that Agency.

(b) In addition to the Assistant Inspector Generals provided for in section 3(d) of this Act, the Inspector General of the Agency for International Development shall, in accordance with applicable laws and regulations governing the civil service, appoint an Assistant Inspector General for Security who shall have the responsibility for supervising the performance of security activities relating to programs and operations of the Agency for International Development.

(c) In addition to the officers and employees provided for in section 6(a)(6) of this Act, members of the Foreign Service may, at the request of the Inspector General of the Agency for International Development, be assigned as employees of the Inspector General. Members of the Foreign Service so assigned shall be responsible solely to the

Inspector General, and the Inspector General (or his or her designee) shall prepare the performance evaluation reports for such members.

(d) In establishing and staffing field offices pursuant to section 6(c) of this Act, the Administrator of the Agency for International Development shall not be bound by overseas personnel ceilings established under the Monitoring Overseas Direct Employment policy.

(e) The Inspector General of the Agency for International Development shall be in addition to the officers provided for in section 624(a) of the Foreign Assistance Act of 1961 [22 U.S.C. § 2384(a)].

(f) As used in this Act, the term "Agency for International Development" includes any successor agency primarily responsible for administering part I of the Foreign Assistance Act of 1961 [22 U.S.C. § 2151 et seq.], an employee of the Inter-American Foundation, and an employee of the African Development Foundation.

§ 8B. Special provisions concerning the Nuclear Regulatory Commission

(a) The Chairman of the Commission may delegate the authority specified in the second sentence of section 3(a) to another member of the Nuclear Regulatory Commission, but shall not delegate such authority to any other officer or employee of the Commission.

(b) Notwithstanding sections 6(a)(7) and (8), the Inspector General of the Nuclear Regulatory Commission is authorized to select, appoint, and employ such officers and employees as may be necessary for carrying out the functions, powers and duties of the Office of Inspector General and to obtain the temporary or intermittent services of experts or consultants or an organization thereof, subject to the applicable laws and regulations that govern such selections, appointments and employment, and the obtaining of such services, within the Nuclear Regulatory Commission.

§ 8C. Special provisions concerning the Federal Deposit Insurance Corporation

(a) Delegation.--The Chairperson of the Federal Deposit Insurance Corporation may delegate the authority specified in the second sentence of section 3(a) to the Vice Chairperson of the Board of Directors of the Federal Deposit Insurance Corporation, but may not delegate such authority to any other officer or employee of the Corporation.

(b) Personnel.--Notwithstanding paragraphs (7) and (8) of section 6(a), the Inspector General of the Federal Deposit Insurance Corporation may select, appoint, and employ such officers and employees as may be necessary for carrying out the functions, powers, and duties of the Office of Inspector General and to obtain the temporary or intermittent services of experts or consultants or an organization of experts or consultants, subject to the applicable laws and regulations that govern such selections, appointments, and employment, and the obtaining of such services, within the Federal Deposit Insurance Corporation.

§ 8D. Special provisions concerning the Department of the Treasury

(a)(1) Notwithstanding the last two sentences of section 3(a), the Inspector General of the Department of the Treasury shall be under the authority, direction, and control of the Secretary of the Treasury with respect to audits or investigations, or the issuance of subpenas, which require access to sensitive information concerning--

(A) ongoing criminal investigations or proceedings;

(B) undercover operations;

(C) the identity of confidential sources, including protected witnesses;

(D) deliberations and decisions on policy matters, including documented information used as a basis for making policy decisions, the disclosure of which could reasonably be expected to have a significant influence on the economy or market behavior;

(E) intelligence or counterintelligence matters; or

(F) other matters the disclosure of which would constitute a serious threat to national security or to the protection of any person or property authorized protection by section 3056 of title 18, United States Code, section 3056A of title 18, United States Code, or any provision of the Presidential Protection Assistance Act of 1976 (18 U.S.C. 3056 note; Public Law 94-524).

(2) With respect to the information described under paragraph (1), the Secretary of the Treasury may prohibit the Inspector General of the Department of the Treasury from carrying out or completing any audit or investigation, or from issuing any subpena, after such Inspector General has decided to initiate, carry out, or complete such audit or investigation or to issue such subpena, if the Secretary determines that such prohibition is necessary to prevent the disclosure of any information described under paragraph (1) or to prevent significant impairment to the national interests of the United States.

(3) If the Secretary of the Treasury exercises any power under paragraph (1) or (2), the Secretary of the Treasury shall notify the Inspector General of the Department of the Treasury in writing stating the reasons for such exercise. Within 30 days after receipt of any such notice, the Inspector General of the Department of the Treasury shall transmit a copy of such notice to the Committees on Governmental Affairs and Finance of the Senate and the Committees on Government Operations and Ways and Means of the House of Representatives, and to other appropriate committees or subcommittees of the Congress.

(4) The Secretary of the Treasury may not exercise any power under paragraph (1) or (2) with respect to the Treasury Inspector General for Tax Administration.

(b)(1) In carrying out the duties and responsibilities specified in this Act, the Inspector General of the Department of the Treasury shall have oversight responsibility for the internal investigations performed by the Office of Internal Affairs of the Tax and Trade Bureau. The head of such office shall promptly report to the Inspector General of the Department of the Treasury the significant activities being carried out by such office.

(2) The Inspector General of the Department of the Treasury shall exercise all duties and responsibilities of an Inspector General for the Department of the Treasury other than the duties and responsibilities exercised by the Treasury Inspector General for Tax Administration.

(3) The Secretary of the Treasury shall establish procedures under which the Inspector General of the Department of the Treasury and the Treasury Inspector General for Tax Administration will--

(A) determine how audits and investigations are allocated in cases of overlapping jurisdiction; and

(B) provide for coordination, cooperation, and efficiency in the conduct of such audits and investigations.

(c) Notwithstanding subsection (b), the Inspector General of the Department of the Treasury may initiate, conduct

and supervise such audits and investigations in the Department of the Treasury (including the bureau referred to in subsection (b)) as the Inspector General of the Department of the Treasury considers appropriate.

(d) If the Inspector General of the Department of the Treasury initiates an audit or investigation under subsection (c) concerning the bureau referred to in subsection (b), the Inspector General of the Department of the Treasury may provide the head of the office of such bureau referred to in subsection (b) with written notice that the Inspector General of the Department of the Treasury has initiated such an audit or investigation. If the Inspector General of the Department of the Treasury issues a notice under the preceding sentence, no other audit or investigation shall be initiated into the matter under audit or investigation by the Inspector General of the Department of the Treasury and any other audit or investigation of such matter shall cease.

(e)(1) The Treasury Inspector General for Tax Administration shall have access to returns and return information, as defined in section 6103(b) of the Internal Revenue Code of 1986 [26 U.S.C. § 6103(b)], only in accordance with the provisions of section 6103 of such Code [26 U.S.C. § 6103] and this Act.

(2) The Internal Revenue Service shall maintain the same system of standardized records or accountings of all requests from the Treasury Inspector General for Tax Administration for inspection or disclosure of returns and return information (including the reasons for and dates of such requests), and of returns and return information inspected or disclosed pursuant to such requests, as described under section 6103(p)(3)(A) of the Internal Revenue Code of 1986 [26 U.S.C. § 6103(p)(3)(A)]. Such system of standardized records or accountings shall also be available for examination in the same manner as provided under section 6103(p)(3) of the Internal Revenue Code of 1986 [26 U.S.C. § 6103(p)(3)].

(3) The Treasury Inspector General for Tax Administration shall be subject to the same safeguards and conditions for receiving returns and return information as are described under section 6103(p)(4) of the Internal Revenue Code of 1986 [26 U.S.C. § 6103(p)(4)].

(f) An audit or investigation conducted by the Inspector General of the Department of the Treasury or the Treasury Inspector General for Tax Administration shall not affect a final decision of the Secretary of the Treasury or his delegate under section 6406 of the Internal Revenue Code of 1986 [26 U.S.C. § 6406].

(g)(1) Any report required to be transmitted by the Secretary of the Treasury to the appropriate committees or subcommittees of the Congress under section 5(d) shall also be transmitted, within the seven-day period specified under such section, to the Committees on Governmental Affairs and Finance of the Senate and the Committees on Government Reform and Oversight and Ways and Means of the House of Representatives.

(2) Any report made by the Treasury Inspector General for Tax Administration that is required to be transmitted by the Secretary of the Treasury to the appropriate committees or subcommittees of Congress under section 5(d) shall also be transmitted, within the 7-day period specified under such subsection, to the Internal Revenue Service Oversight Board and the Commissioner of Internal Revenue.

(h) The Treasury Inspector General for Tax Administration shall exercise all duties and responsibilities of an Inspector General of an establishment with respect to the Department of the Treasury and the Secretary of the Treasury on all matters relating to the Internal Revenue Service. The Treasury Inspector General for Tax Administration shall have sole authority under this Act to conduct an audit or investigation of the Internal Revenue Service Oversight Board and the Chief Counsel for the Internal Revenue Service.

(i) In addition to the requirements of the first sentence of section 3(a), the Treasury Inspector General for Tax Administration should have demonstrated ability to lead a large and complex organization.

(j) An individual appointed to the position of Treasury Inspector General for Tax Administration, the Assistant Inspector General for Auditing of the Office of the Treasury Inspector General for Tax Administration under section 3(d)(1), the Assistant Inspector General for Investigations of the Office of the Treasury Inspector General for Tax Administration under section 3(d)(2), or any position of Deputy Inspector General of the Office of the Treasury Inspector General for Tax Administration may not be an employee of the Internal Revenue Service--

(1) during the 2-year period preceding the date of appointment to such position; or

(2) during the 5-year period following the date such individual ends service in such position.

(k)(1) In addition to the duties and responsibilities exercised by an inspector general of an establishment, the Treasury Inspector General for Tax Administration--

(A) shall have the duty to enforce criminal provisions under section 7608(b) of the Internal Revenue Code of 1986 [26 U.S.C. § 7608(b)];

(B) in addition to the functions authorized under section 7608(b)(2) of such Code [26 U.S.C. § 7608(b)(2)], may carry firearms;

(C) shall be responsible for protecting the Internal Revenue Service against external attempts to corrupt or threaten employees of the Internal Revenue Service, but shall not be responsible for the conducting of background checks and the providing of protection to the Commissioner of Internal Revenue; and

(D) may designate any employee in the Office of the Treasury Inspector General for Tax Administration to enforce such laws and perform such functions referred to under subparagraphs (A), (B), and (C).

(2)(A) In performing a law enforcement function under paragraph (1), the Treasury Inspector General for Tax Administration shall report any reasonable grounds to believe there has been a violation of Federal criminal law to the Attorney General at an appropriate time as determined by the Treasury Inspector General for Tax Administration, notwithstanding section 4(d).

(B) In the administration of section 5(d) and subsection (g)(2) of this section, the Secretary of the Treasury may transmit the required report with respect to the Treasury Inspector General for Tax Administration at an appropriate time as determined by the Secretary, if the problem, abuse, or deficiency relates to--

(i) the performance of a law enforcement function under paragraph (1); and

(ii) sensitive information concerning matters under subsection (a)(1)(A) through (F).

(3) Nothing in this subsection shall be construed to affect the authority of any other person to carry out or enforce any provision specified in paragraph (1).

(l)(1) The Commissioner of Internal Revenue or the Internal Revenue Service Oversight Board may request, in writing, the Treasury Inspector General for Tax Administration to conduct an audit or investigation relating to the Internal Revenue Service. If the Treasury Inspector General for Tax Administration determines not to conduct such audit or investigation, the Inspector General shall timely provide a written explanation for such determination to the person making the request.

(2)(A) Any final report of an audit conducted by the Treasury Inspector General for Tax Administration shall be

timely submitted by the Inspector General to the Commissioner of Internal Revenue and the Internal Revenue Service Oversight Board.

(B) The Treasury Inspector General for Tax Administration shall periodically submit to the Commissioner and Board a list of investigations for which a final report has been completed by the Inspector General and shall provide a copy of any such report upon request of the Commissioner or Board.

(C) This paragraph applies regardless of whether the applicable audit or investigation is requested under paragraph (1).

§ 8E. Special provisions concerning the Department of Justice

(a)(1) Notwithstanding the last two sentences of section 3(a), the Inspector General shall be under the authority, direction, and control of the Attorney General with respect to audits or investigations, or the issuance of subpenas, which require access to sensitive information concerning--

(A) ongoing civil or criminal investigations or proceedings;

(B) undercover operations;

(C) the identity of confidential sources, including protected witnesses;

(D) intelligence or counterintelligence matters; or

(E) other matters the disclosure of which would constitute a serious threat to national security.

(2) With respect to the information described under paragraph (1), the Attorney General may prohibit the Inspector General from carrying out or completing any audit or investigation, or from issuing any subpena, after such Inspector General has decided to initiate, carry out, or complete such audit or investigation or to issue such subpena, if the Attorney General determines that such prohibition is necessary to prevent the disclosure of any information described under paragraph (1) or to prevent the significant impairment to the national interests of the United States.

(3) If the Attorney General exercises any power under paragraph (1) or (2), the Attorney General shall notify the Inspector General in writing stating the reasons for such exercise. Within 30 days after receipt of any such notice, the Inspector General shall transmit a copy of such notice to the Committees on Governmental Affairs and Judiciary of the Senate and the Committees on Government Operations and Judiciary of the House of Representatives, and to other appropriate committees or subcommittees of the Congress.

(b) In carrying out the duties and responsibilities specified in this Act, the Inspector General of the Department of Justice--

(1) may initiate, conduct and supervise such audits and investigations in the Department of Justice as the Inspector General considers appropriate;

(2) except as specified in subsection (a) and paragraph (3), may investigate allegations of criminal wrongdoing or administrative misconduct by an employee of the Department of Justice, or may, in the discretion of the Inspector General, refer such allegations to the Office of Professional Responsibility or the internal affairs office of the appropriate component of the Department of Justice;

(3) shall refer to the Counsel, Office of Professional Responsibility of the Department of Justice, allegations of misconduct involving Department attorneys, investigators, or law enforcement personnel, where the allegations relate to the exercise of the authority of an attorney to investigate, litigate, or provide legal advice, except that no such referral shall be made if the attorney is employed in the Office of Professional Responsibility;

(4) may investigate allegations of criminal wrongdoing or administrative misconduct by a person who is the head of any agency or component of the Department of Justice; and

(5) shall forward the results of any investigation conducted under paragraph (4), along with any appropriate recommendation for disciplinary action, to the Attorney General.

(c) Any report required to be transmitted by the Attorney General to the appropriate committees or subcommittees of the Congress under section 5(d) shall also be transmitted, within the seven-day period specified under such section, to the Committees on the Judiciary and Governmental Affairs of the Senate and the Committees on the Judiciary and Government Operations of the House of Representatives.

(d) The Attorney General shall ensure by regulation that any component of the Department of Justice receiving a nonfrivolous allegation of criminal wrongdoing or administrative misconduct by an employee of the Department of Justice, except with respect to allegations described in subsection (b)(3), shall report that information to the Inspector General.

§ 8F. Special provisions concerning the Corporation for National and Community Service

(a) Notwithstanding the provisions of paragraphs (7) and (8) of section 6(a), it is within the exclusive jurisdiction of the Inspector General of the Corporation for National and Community Service to--

(1) appoint and determine the compensation of such officers and employees in accordance with section 195(b) of the National and Community Service Act of 1990; and

(2) procure the temporary and intermittent services of and compensate such experts and consultants, in accordance with section 3109(b) of title 5, United States Code, as may be necessary to carry out the functions, powers, and duties of the Inspector General.

(b) No later than the date on which the Chief Executive Officer of the Corporation for National and Community Service transmits any report to the Congress under subsection (a) or (b) of section 5, the Chief Executive Officer shall transmit such report to the Board of Directors of such Corporation.

(c) No later than the date on which the Chief Executive Officer of the Corporation for National and Community Service transmits a report described under section 5(b) to the Board of Directors as provided under subsection (b) of this section, the Chief Executive Officer shall also transmit any audit report which is described in the statement required under section 5(b)(4) to the Board of Directors. All such audit reports shall be placed on the agenda for review at the next scheduled meeting of the Board of Directors following such transmittal. The Chief Executive Officer of the Corporation shall be present at such meeting to provide any information relating to such audit reports.

(d) No later than the date on which the Inspector General of the Corporation for National and Community Service reports a problem, abuse, or deficiency under section 5(d) to the Chief Executive Officer of the Corporation, the Chief Executive Officer shall report such problem, abuse, or deficiency to the Board of Directors.

§ 8G. Requirements for Federal entities and designated Federal entities

(a) Notwithstanding section 12 of this Act, as used in this section--

(1) the term "Federal entity" means any Government corporation (within the meaning of section 103(1) of title 5, United States Code), any Government controlled corporation (within the meaning of section 103(2) of such title), or any other entity in the Executive branch of the Government, or any independent regulatory agency, but does not include--

(A) an establishment (as defined under section 12(2) of this Act) or part of an establishment;

(B) a designated Federal entity (as defined under paragraph (2) of this subsection) or part of a designated Federal entity;

(C) the Executive Office of the President;

(D) the Central Intelligence Agency;

(E) the Government Accountability Office; or

(F) any entity in the judicial or legislative branches of the Government, including the Administrative Office of the United States Courts and the Architect of the Capitol and any activities under the direction of the Architect of the Capitol;

(2) the term "designated Federal entity" means Amtrak, the Appalachian Regional Commission, the Board of Governors of the Federal Reserve System and the Bureau of Consumer Financial Protection, the Board for International Broadcasting, the Commodity Futures Trading Commission, the Consumer Product Safety Commission, the Corporation for Public Broadcasting, the Defense Intelligence Agency, the Denali Commission, the Equal Employment Opportunity Commission, the Farm Credit Administration, the Federal Communications Commission, the Federal Election Commission, the Election Assistance Commission, the Federal Housing Finance Board, the Federal Labor Relations Authority, the Federal Maritime Commission, the Federal Trade Commission, the Legal Services Corporation, the National Archives and Records Administration, the National Credit Union Administration, the National Endowment for the Arts, the National Endowment for the Humanities, the National Geospatial-Intelligence Agency, the National Labor Relations Board, the National Reconnaissance Office, the National Security Agency, the National Science Foundation, the Panama Canal Commission, the Peace Corps, the Pension Benefit Guaranty Corporation, the Securities and Exchange Commission, the Smithsonian Institution, the United States International Trade Commission, the Postal Regulatory Commission, and the United States Postal Service;

(3) the term "head of the Federal entity" means any person or persons designated by statute as the head of a Federal entity, and if no such designation exists, the chief policymaking officer or board of a Federal entity as identified in the list published pursuant to subsection (h)(1) of this section;

(4) the term "head of the designated Federal entity" means the board or commission of the designated Federal entity, or in the event the designated Federal entity does not have a board or commission, any person or persons designated by statute as the head of a designated Federal entity and if no such designation exists, the chief policymaking officer or board of a designated Federal entity as identified in the list published pursuant to subsection (h)(1) of this section, except that--

(A) with respect to the National Science Foundation, such term means the National Science Board;

(B) with respect to the United States Postal Service, such term means the Governors (within the meaning of section 102(3) of title 39, United States Code);

(C) with respect to the Federal Labor Relations Authority, such term means the members of the Authority (described under section 7104 of title 5, United States Code);

(D) with respect to the National Archives and Records Administration, such term means the Archivist of the United States;

(E) with respect to the National Credit Union Administration, such term means the National Credit Union Administration Board (described under section 102 of the Federal Credit Union Act (12 U.S.C. 1752a);

(F) with respect to the National Endowment of the Arts, such term means the National Council on the Arts;

(G) with respect to the National Endowment for the Humanities, such term means the National Council on the Humanities; and

(H) with respect to the Peace Corps, such term means the Director of the Peace Corps;

(5) the term "Office of Inspector General" means an Office of Inspector General of a designated Federal entity; and

(6) the term "Inspector General" means an Inspector General of a designated Federal entity.

(b) No later than 180 days after the date of the enactment of this section [Oct. 18, 1988], there shall be established and maintained in each designated Federal entity an Office of Inspector General. The head of the designated Federal entity shall transfer to such office the offices, units, or other components, and the functions, powers, or duties thereof, that such head determines are properly related to the functions of the Office of Inspector General and would, if so transferred, further the purposes of this section. There shall not be transferred to such office any program operating responsibilities.

(c) Except as provided under subsection (f) of this section, the Inspector General shall be appointed by the head of the designated Federal entity in accordance with the applicable laws and regulations governing appointments within the designated Federal entity. Each Inspector General shall be appointed without regard to political affiliation and solely on the basis of integrity and demonstrated ability in accounting, auditing, financial analysis, law, management analysis, public administration, or investigations. For purposes of implementing this section, the Chairman of the Board of Governors of the Federal Reserve System shall appoint the Inspector General of the Board of Governors of the Federal Reserve System and the Bureau of Consumer Financial Protection. The Inspector General of the Board of Governors of the Federal Reserve System and the Bureau of Consumer Financial Protection shall have all of the authorities and responsibilities provided by this Act with respect to the Bureau of Consumer Financial Protection, as if the Bureau were part of the Board of Governors of the Federal Reserve System.

(d)(1) Each Inspector General shall report to and be under the general supervision of the head of the designated Federal entity, but shall not report to, or be subject to supervision by, any other officer or employee of such designated Federal entity. Except as provided in paragraph (2), the head of the designated Federal entity shall not

prevent or prohibit the Inspector General from initiating, carrying out, or completing any audit or investigation, or from issuing any subpena during the course of any audit or investigation.

(2)(A) The Secretary of Defense, in consultation with the Director of National Intelligence, may prohibit the inspector general of an element of the intelligence community specified in subparagraph (D) from initiating, carrying out, or completing any audit or investigation if the Secretary determines that the prohibition is necessary to protect vital national security interests of the United States.

(B) If the Secretary exercises the authority under subparagraph (A), the Secretary shall submit to the committees of Congress specified in subparagraph (E) an appropriately classified statement of the reasons for the exercise of such authority not later than 7 days after the exercise of such authority.

(C) At the same time the Secretary submits under subparagraph (B) a statement on the exercise of the authority in subparagraph (A) to the committees of Congress specified in subparagraph (E), the Secretary shall notify the inspector general of such element of the submittal of such statement and, to the extent consistent with the protection of intelligence sources and methods, provide such inspector general with a copy of such statement. Such inspector general may submit to such committees of Congress any comments on a notice or statement received by the inspector general under this subparagraph that the inspector general considers appropriate.

(D) The elements of the intelligence community specified in this subparagraph are as follows:

(i) The Defense Intelligence Agency.

(ii) The National Geospatial-Intelligence Agency.

(iii) The National Reconnaissance Office.

(iv) The National Security Agency.

(E) The committees of Congress specified in this subparagraph are--

(i) the Committee on Armed Services and the Select Committee on Intelligence of the Senate; and

(ii) the Committee on Armed Services and the Permanent Select Committee on Intelligence of the House of Representatives.

(e)(1) In the case of a designated Federal entity for which a board or commission is the head of the designated Federal entity, a removal under this subsection may only be made upon the written concurrence of a 2/3 majority of the board or commission.

(2) If an Inspector General is removed from office or is transferred to another position or location within a designated Federal entity, the head of the designated Federal entity shall communicate in writing the reasons for any such removal or transfer to both Houses of Congress, not later than 30 days before the removal or transfer. Nothing in this subsection shall prohibit a personnel action otherwise authorized by law, other than transfer or removal.

(f)(1) For purposes of carrying out subsection (c) with respect to the United States Postal Service, the appointment provisions of section 202(e) of title 39, United States Code, shall be applied.

(2) In carrying out the duties and responsibilities specified in this Act, the Inspector General of the United States Postal Service (hereinafter in this subsection referred to as the "Inspector General") shall have oversight responsibility for all activities of the Postal Inspection Service, including any internal investigation performed by the Postal Inspection Service. The Chief Postal Inspector shall promptly report the significant activities being carried out by the Postal Inspection Service to such Inspector General.

(3)(A)(i) Notwithstanding subsection (d), the Inspector General shall be under the authority, direction, and control of the Governors with respect to audits or investigations, or the issuance of subpoenas, which require access to sensitive information concerning--

(I) ongoing civil or criminal investigations or proceedings;

(II) undercover operations;

(III) the identity of confidential sources, including protected witnesses;

(IV) intelligence or counterintelligence matters; or

(V) other matters the disclosure of which would constitute a serious threat to national security.

(ii) With respect to the information described under clause (i), the Governors may prohibit the Inspector General from carrying out or completing any audit or investigation, or from issuing any subpoena, after such Inspector General has decided to initiate, carry out, or complete such audit or investigation or to issue such subpoena, if the Governors determine that such prohibition is necessary to prevent the disclosure of any information described under clause (i) or to prevent the significant impairment to the national interests of the United States.

(iii) If the Governors exercise any power under clause (i) or (ii), the Governors shall notify the Inspector General in writing stating the reasons for such exercise. Within 30 days after receipt of any such notice, the Inspector General shall transmit a copy of such notice to the Committee on Governmental Affairs of the Senate and the Committee on Government Reform and Oversight of the House of Representatives, and to other appropriate committees or subcommittees of the Congress.

(B) In carrying out the duties and responsibilities specified in this Act, the Inspector General--

(i) may initiate, conduct and supervise such audits and investigations in the United States Postal Service as the Inspector General considers appropriate; and

(ii) shall give particular regard to the activities of the Postal Inspection Service with a view toward avoiding duplication and insuring effective coordination and cooperation.

(C) Any report required to be transmitted by the Governors to the appropriate committees or subcommittees of the Congress under section 5(d) shall also be transmitted, within the seven-day period specified under such section, to the Committee on Governmental Affairs of the Senate and the Committee on Government Reform and Oversight of the House of Representatives.

(4) Nothing in this Act shall restrict, eliminate, or otherwise adversely affect any of the rights, privileges, or benefits of either employees of the United States Postal Service, or labor organizations representing employees of the United States Postal Service, under chapter 12 of title 39, United States Code, the National Labor Relations Act, any handbook or manual affecting employee labor relations with the United States Postal Service, or any

collective bargaining agreement.

(5) As used in this subsection, the term "Governors" has the meaning given such term by section 102(3) of title 39, United States Code.

(6) There are authorized to be appropriated, out of the Postal Service Fund, such sums as may be necessary for the Office of Inspector General of the United States Postal Service.

(g)(1) Sections 4, 5, 6 (other than subsections (a)(7) and (a)(8) thereof), and 7 of this Act shall apply to each Inspector General and Office of Inspector General of a designated Federal entity and such sections shall be applied to each designated Federal entity and head of the designated Federal entity (as defined under subsection (a)) by substituting--

(A) "designated Federal entity" for "establishment"; and

(B) "head of the designated Federal entity" for "head of the establishment".

(2) In addition to the other authorities specified in this Act, an Inspector General is authorized to select, appoint, and employ such officers and employees as may be necessary for carrying out the functions, powers, and duties of the Office of Inspector General and to obtain the temporary or intermittent services of experts or consultants or an organization thereof, subject to the applicable laws and regulations that govern such selections, appointments, and employment, and the obtaining of such services, within the designated Federal entity.

(3) Notwithstanding the last sentence of subsection (d) of this section, the provisions of subsection (a) of section 8C (other than the provisions of subparagraphs (A), (B), (C), and (E) of subsection (a)(1)) shall apply to the Inspector General of the Board of Governors of the Federal Reserve System and the Bureau of Consumer Financial Protection and the Chairman of the Board of Governors of the Federal Reserve System in the same manner as such provisions apply to the Inspector General of the Department of the Treasury and the Secretary of the Treasury, respectively.

(4) Each Inspector General shall--

(A) in accordance with applicable laws and regulations governing appointments within the designated Federal entity, appoint a Counsel to the Inspector General who shall report to the Inspector General;

(B) obtain the services of a counsel appointed by and directly reporting to another Inspector General on a reimbursable basis; or

(C) obtain the services of appropriate staff of the Council of the Inspectors General on Integrity and Efficiency on a reimbursable basis.

(h)(1) No later than April 30, 1989, and annually thereafter, the Director of the Office of Management and Budget, after consultation with the Comptroller General of the United States, shall publish in the Federal Register a list of the Federal entities and designated Federal entities and if the designated Federal entity is not a board or commission, include the head of each such entity (as defined under subsection (a) of this section).

(2) Beginning on October 31, 1989, and on October 31 of each succeeding calendar year, the head of each Federal entity (as defined under subsection (a) of this section) shall prepare and transmit to the Director of the Office of Management and Budget and to each House of the Congress a report which--

(A) states whether there has been established in the Federal entity an office that meets the requirements of this section;

(B) specifies the actions taken by the Federal entity otherwise to ensure that audits are conducted of its programs and operations in accordance with the standards for audit of governmental organizations, programs, activities, and functions issued by the Comptroller General of the United States, and includes a list of each audit report completed by a Federal or non-Federal auditor during the reporting period and a summary of any particularly significant findings; and

(C) summarizes any matters relating to the personnel, programs, and operations of the Federal entity referred to prosecutive authorities, including a summary description of any preliminary investigation conducted by or at the request of the Federal entity concerning these matters, and the prosecutions and convictions which have resulted.

§ 8H. Additional Provisions with Respect to Inspectors General of the Intelligence Community--

(a)(1)(A) An employee of the Defense Intelligence Agency, the National Geospatial-Intelligence Agency, the National Reconnaissance Office, or the National Security Agency, or of a contractor of any of those Agencies, who intends to report to Congress a complaint or information with respect to an urgent concern may report the complaint or information to the Inspector General of the Department of Defense (or designee).

(B) An employee of the Federal Bureau of Investigation, or of a contractor of the Bureau, who intends to report to Congress a complaint or information with respect to an urgent concern may report the complaint or information to the Inspector General of the Department of Justice (or designee).

(C) Any other employee of, or contractor to, an executive agency, or element or unit thereof, determined by the President under section 2302(a)(2)(C)(ii) of title 5, United States Code, to have as its principal function the conduct of foreign intelligence or counterintelligence activities, who intends to report to Congress a complaint or information with respect to an urgent concern may report the complaint or information to the appropriate Inspector General (or designee) under this Act or section 17 of the Central Intelligence Agency Act of 1949 [50 U.S.C. § 403a et seq.].

(2) If a designee of an Inspector General under this section receives a complaint or information of an employee with respect to an urgent concern, that designee shall report the complaint or information to the Inspector General within 7 calendar days of receipt.

(3) The Inspectors General of the Defense Intelligence Agency, the National Geospatial-Intelligence Agency, the National Reconnaissance Office, and the National Security Agency shall be designees of the Inspector General of the Department of Defense for purposes of this section.

(b) Not later than the end of the 14-calendar day period beginning on the date of receipt of an employee complaint or information under subsection (a), the Inspector General shall determine whether the complaint or information appears credible. Upon making such a determination, the Inspector General shall transmit to the head of the establishment notice of that determination, together with the complaint or information.

(c) Upon receipt of a transmittal from the Inspector General under subsection (b), the head of the establishment shall, within 7 calendar days of such receipt, forward such transmittal to the intelligence committees, together with any comments the head of the establishment considers appropriate.

(d)(1) If the Inspector General does not find credible under subsection (b) a complaint or information submitted to the Inspector General under subsection (a), or does not transmit the complaint or information to the head of the establishment in accurate form under subsection (b), the employee (subject to paragraph (2)) may submit the complaint or information to Congress by contacting either or both of the intelligence committees directly.

(2) The employee may contact the intelligence committees directly as described in paragraph (1) only if the employee--

(A) before making such a contact, furnishes to the head of the establishment, through the Inspector General, a statement of the employee's complaint or information and notice of the employee's intent to contact the intelligence committees directly; and

(B) obtains and follows from the head of the establishment, through the Inspector General, direction on how to contact the intelligence committees in accordance with appropriate security practices.

(3) A member or employee of one of the intelligence committees who receives a complaint or information under paragraph (1) does so in that member or employee's official capacity as a member or employee of that committee.

(e) The Inspector General shall notify an employee who reports a complaint or information under this section of each action taken under this section with respect to the complaint or information. Such notice shall be provided not later than 3 days after any such action is taken.

(f) An action taken by the head of an establishment or an Inspector General under subsections (a) through (e) shall not be subject to judicial review.

(g)(1) The Inspector General of the Defense Intelligence Agency, the National Geospatial-Intelligence Agency, the National Reconnaissance Office, and the National Security Agency shall each submit to the congressional intelligence committees each year a report that sets forth the following:

(A) The personnel and funds requested by such Inspector General for the fiscal year beginning in such year for the activities of the office of such Inspector General in such fiscal year.

(B) The plan of such Inspector General for such activities, including the programs and activities scheduled for review by the office of such Inspector General during such fiscal year.

(C) An assessment of the current ability of such Inspector General to hire and retain qualified personnel for the office of such Inspector General.

(D) Any matters that such Inspector General considers appropriate regarding the independence and effectiveness of the office of such Inspector General.

(2) The submittal date for a report under paragraph (1) each year shall be the date provided in section 507 of the National Security Act of 1947.

(3) In this subsection, the term "congressional intelligence committees" shall have the meaning given that term in section 3 of the National Security Act of 1947 (50 U.S.C. 401a).

(h) In this section:

(1) The term "urgent concern" means any of the following:

(A) A serious or flagrant problem, abuse, violation of law or Executive order, or deficiency relating to the funding, administration, or operations of an intelligence activity involving classified information, but does not include differences of opinions concerning public policy matters.

(B) A false statement to Congress, or a willful withholding from Congress, on an issue of material fact relating to the funding, administration, or operation of an intelligence activity.

(C) An action, including a personnel action described in section 2302(a)(2)(A) of Title 5, constituting reprisal or threat of reprisal prohibited under section 7(c) in response to an employee's reporting an urgent concern in accordance with this section.

(2) The term "intelligence committees" means the Permanent Select Committee on Intelligence of the House of Representatives and the Select Committee on Intelligence of the Senate.

§ 8I. Special provisions concerning the Department of Homeland Security

(a)(1) Notwithstanding the last two sentences of section 3(a), the Inspector General of the Department of Homeland Security shall be under the authority, direction, and control of the Secretary of Homeland Security with respect to audits or investigations, or the issuance of subpoenas, that require access to sensitive information concerning--

(A) intelligence, counterintelligence, or counterterrorism matters;

(B) ongoing criminal investigations or proceedings;

(C) undercover operations;

(D) the identity of confidential sources, including protected witnesses;

(E) other matters the disclosure of which would, in the Secretary's judgment, constitute a serious threat to the protection of any person or property authorized protection by section 3056 of Title 18, section 3056A of title 18, or any provision of the Presidential Protection Assistance Act of 1976 (18 U.S.C. 3056 note); or

(F) other matters the disclosure of which would constitute a serious threat to national security.

(2) With respect to the information described in paragraph (1), the Secretary of Homeland Security may prohibit the Inspector General of the Department of Homeland Security from carrying out or completing any audit or investigation, or from issuing any subpoena, after such Inspector General has decided to initiate, carry out, or complete such audit or investigation or to issue such subpoena, if the Secretary determines that such prohibition is necessary to prevent the disclosure of any information described in paragraph (1), to preserve the national security, or to prevent a significant impairment to the interests of the United States.

(3) If the Secretary of Homeland Security exercises any power under paragraph (1) or (2), the Secretary shall notify the Inspector General of the Department of Homeland Security in writing within seven days stating the reasons for such exercise. Within 30 days after receipt of any such notice, the Inspector General shall transmit to the President of the Senate, the Speaker of the House of Representatives, and appropriate committees and subcommittees of Congress the following:

(A) A copy of such notice.

(B) A written response to such notice that includes a statement regarding whether the Inspector General agrees or disagrees with such exercise, and the reasons for any disagreement.

(b) The exercise of authority by the Secretary described in paragraph (2) should not be construed as limiting the right of Congress or any committee of Congress to access any information it seeks.

(c) Subject to the conditions established in subsections (a) and (b) above, in carrying out the duties and responsibilities specified in this Act, the Inspector General of the Department of Homeland Security may initiate, conduct, and supervise such audits and investigations in the Department of Homeland Security as the Inspector General considers appropriate.

(d) Any report required to be transmitted by the Secretary of Homeland Security to the appropriate committees or subcommittees of Congress under section 5(d) shall be transmitted, within the seven-day period specified under such section, to the President of the Senate, the Speaker of the House of Representatives, and appropriate committees and subcommittees of Congress.

(e) Notwithstanding any other provision of law, in carrying out the duties and responsibilities specified in this Act, the Inspector General of the Department of Homeland Security shall have oversight responsibility for the internal investigations performed by the Office of Internal Affairs of the United States Customs Service, the Office of Inspections of the United States Secret Service, the Bureau of Border Security, and the Bureau of Citizenship and Immigration Services. The head of each such office or bureau shall promptly report to the Inspector General the significant activities being carried out by such office or bureau.

(f)(1) The Inspector General of the Department of Homeland Security shall designate a senior official within the Office of Inspector General, who shall be a career member of the civil service at the equivalent to the GS-15 level or a career member of the Senior Executive Service, to perform the functions described in paragraph (2).

(2) The senior official designated under paragraph (1) shall--

(A) coordinate the activities of the Office of Inspector General with respect to investigations of abuses of civil rights or civil liberties;

(B) receive and review complaints and information from any source alleging abuses of civil rights and civil liberties by employees or officials of the Department and employees or officials of independent contractors or grantees of the Department;

(C) initiate investigations of alleged abuses of civil rights or civil liberties by employees or officials of the Department and employees or officials of independent contractors or grantees of the Department;

(D) ensure that personnel within the Office of Inspector General receive sufficient training to conduct effective civil rights and civil liberties investigations;

(E) consult with the Officer for Civil Rights and Civil Liberties regarding--

(i) alleged abuses of civil rights or civil liberties; and

(ii) any policy recommendations regarding civil rights and civil liberties that may be founded upon an investigation by the Office of Inspector General;

(F) provide the Officer for Civil Rights and Civil Liberties with information regarding the outcome of investigations of alleged abuses of civil rights and civil liberties;

(G) refer civil rights and civil liberties matters that the Inspector General decides not to investigate to the Officer for Civil Rights and Civil Liberties;

(H) ensure that the Office of the Inspector General publicizes and provides convenient public access to information regarding--

(i) the procedure to file complaints or comments concerning civil rights and civil liberties matters; and

(ii) the status of corrective actions taken by the Department in response to Office of the Inspector General reports; and

(I) inform the Officer for Civil Rights and Civil Liberties of any weaknesses, problems, and deficiencies within the Department relating to civil rights or civil liberties.

§ 8J. Rule of construction of special provisions

The special provisions under section 8, 8A, 8B, 8C, 8D, 8E, 8F, or 8H of this Act relate only to the establishment named in such section and no inference shall be drawn from the presence or absence of a provision in any such section with respect to an establishment not named in such section or with respect to a designated Federal entity as defined under section 8G(a).

§ 8K. Authority to establish Inspector General of the Office of the Director of National Intelligence

If the Director of National Intelligence determines that an Office of Inspector General would be beneficial to improving the operations and effectiveness of the Office of the Director of National Intelligence, the Director of National Intelligence is authorized to establish, with any of the duties, responsibilities, and authorities set forth in this Act, an Office of Inspector General.

§ 8L. Information on websites of offices of Inspectors General

(a) Direct links to Inspectors General offices.--

(1) In general.--Each agency shall establish and maintain on the homepage of the website of that agency, a direct link to the website of the Office of the Inspector General of that agency.

(2) Accessibility.--The direct link under paragraph (1) shall be obvious and facilitate accessibility to the website of the Office of the Inspector General.

(b) Requirements for Inspectors General websites.--

(1) Posting of reports and audits.--The Inspector General of each agency shall--

(A) not later than 3 days after any report or audit (or portion of any report or audit) is made publicly available, post that report or audit (or portion of that report or audit) on the website of the Office of Inspector General; and

(B) ensure that any posted report or audit (or portion of that report or audit) described under subparagraph (A)--

(i) is easily accessible from a direct link on the homepage of the website of the Office of the Inspector General;

(ii) includes a summary of the findings of the Inspector General; and

(iii) is in a format that--

(I) is searchable and downloadable; and

(II) facilitates printing by individuals of the public accessing the website.

(2) Reporting of fraud, waste, and abuse.--

(A) In general.--The Inspector General of each agency shall establish and maintain a direct link on the homepage of the website of the Office of the Inspector General for individuals to report fraud, waste, and abuse. Individuals reporting fraud, waste, or abuse using the direct link established under this paragraph shall not be required to provide personally identifying information relating to that individual.

(B) Anonymity.--The Inspector General of each agency shall not disclose the identity of any individual making a report under this paragraph without the consent of the individual unless the Inspector General determines that such a disclosure is unavoidable during the course of the investigation.

§ 9. Transfer of functions

(a) There shall be transferred--

(1) to the Office of Inspector General--

(A) of the Department of Agriculture, the offices of that department referred to as the "Office of Investigation" and the "Office of Audit";

(B) of the Department of Commerce, the offices of that department referred to as the "Office of Audits" and the "Investigations and Inspections Staff" and that portion of the office referred to as the "Office of Investigations and Security" which has responsibility for investigation of alleged criminal violations and program abuse;

(C) of the Department of Defense, the offices of that department referred to as the "Defense Audit Service" and the "Office of Inspector General, Defense Logistics Agency", and that portion of the office of that department referred to as the "Defense Investigative Service" which has responsibility for the investigation of alleged criminal violations;

(D) of the Department of Education, all functions of the Inspector General of Health, Education, and Welfare or of the Office of Inspector General of Health, Education, and Welfare relating to functions transferred by section 301 of the Department of Education Organization Act [20 U.S.C. § 3441];

(E) of the Department of Energy, the Office of Inspector General (as established by section 208 of the Department of Energy Organization Act);

(F) of the Department of Health and Human Services, the Office of Inspector General (as established by title II of Public Law 94-505);

(G) of the Department of Housing and Urban Development, the office of that department referred to as the "Office of Inspector General";

(H) of the Department of the Interior, the office of that department referred to as the "Office of Audit and Investigation";

(I) of the Department of Justice, the offices of that Department referred to as (i) the "Audit Staff, Justice Management Division", (ii) the "Policy and Procedures Branch, Office of the Comptroller, Immigration and Naturalization Service", the "Office of Professional Responsibility, Immigration and Naturalization Service", and the "Office of Program Inspections, Immigration and Naturalization Service", (iii) the "Office of Internal Inspection, United States Marshals Service", (iv) the "Financial Audit Section, Office of Financial Management, Bureau of Prisons" and the "Office of Inspections, Bureau of Prisons", and (v) from the Drug Enforcement Administration, that portion of the "Office of Inspections" which is engaged in internal audit activities, and that portion of the "Office of Planning and Evaluation" which is engaged in program review activities;

(J) of the Department of Labor, the office of that department referred to as the "Office of Special Investigations";

(K) of the Department of Transportation, the offices of that department referred to as the "Office of Investigations and Security" and the "Office of Audit" of the Department, the "Offices of Investigations and Security, Federal Aviation Administration", and "External Audit Divisions, Federal Aviation Administration", the "Investigations Division and the External Audit Division of the Office of Program Review and Investigation, Federal Highway Administration", and the "Office of Program Audits, Urban Mass Transportation Administration";

(L)(i) of the Department of the Treasury, the office of that department referred to as the "Office of Inspector General", and, notwithstanding any other provision of law, that portion of each of the offices of that department referred to as the "Office of Internal Affairs, Tax and Trade Bureau", the "Office of Internal Affairs, United States Customs Service", and the "Office of Inspections, United States Secret Service" which is engaged in internal audit activities; and

(ii) of the Treasury Inspector General for Tax Administration, effective 180 days after the date of the enactment of the Internal Revenue Service Restructuring and Reform Act of 1998, the Office of Chief Inspector of the Internal Revenue Service;

(M) of the Environmental Protection Agency, the offices of that agency referred to as the "Office of Audit" and the "Security and Inspection Division";

(N) of the Federal Emergency Management Agency, the office of that agency referred to as the "Office of Inspector General";

(O) of the General Services Administration, the offices of that agency referred to as the "Office of Audits" and the "Office of Investigations";

(P) of the National Aeronautics and Space Administration, the offices of that agency referred to as the "Management Audit Office" and the "Office of Inspections and Security";

(Q) of the Nuclear Regulatory Commission, the office of that commission referred to as the "Office of Inspector and Auditor";

(R) of the Office of Personnel Management, the offices of that agency referred to as the "Office of Inspector General", the "Insurance Audits Division, Retirement and Insurance Group", and the "Analysis and Evaluation Division, Administration Group";

(S) of the Railroad Retirement Board, the Office of Inspector General (as established by section 23 of the Railroad Retirement Act of 1974);

(T) of the Small Business Administration, the office of that agency referred to as the "Office of Audits and Investigations";

(U) of the Veterans' Administration, the offices of that agency referred to as the "Office of Audits" and the "Office of Investigations"; and

(V) of the Corporation for National and Community Service, the Office of Inspector General of ACTION;

(W) of the Social Security Administration, the functions of the Inspector General of the Department of Health and Human Services which are transferred to the Social Security Administration by the Social Security Independence and Program Improvements Act of 1994 (other than functions performed pursuant to section 105(a)(2) of such Act), except that such transfers shall be made in accordance with the provisions of such Act and shall not be subject to subsections (b) through (d) of this section; and

(2) to the Office of the Inspector General, such other offices or agencies, or functions, powers, or duties thereof, as the head of the establishment involved may determine are properly related to the functions of the Office and would, if so transferred, further the purposes of this Act, except that there shall not be transferred to an Inspector General under paragraph (2) program operating responsibilities.

(b) The personnel, assets, liabilities, contracts, property, records, and unexpended balances of appropriations, authorizations, allocations, and other funds employed, held, used, arising from, available or to be made available, of any office or agency the functions, powers, and duties of which are transferred under subsection (a) are hereby transferred to the applicable Office of Inspector General.

(c) Personnel transferred pursuant to subsection (b) shall be transferred in accordance with applicable laws and regulations relating to the transfer of functions except that the classification and compensation of such personnel shall not be reduced for one year after such transfer.

(d) In any case where all the functions, powers, and duties of any office or agency are transferred pursuant to this subsection, such office or agency shall lapse. Any person who, on the effective date of this Act [Oct. 1, 1978], held a position compensated in accordance with the General Schedule, and who, without a break in service, is appointed in an Office of Inspector General to a position having duties comparable to those performed immediately preceding such appointment shall continue to be compensated in the new position at not less than the

rate provided for the previous position, for the duration of service in the new position.

§ 10. Conforming and technical amendments

[Section amended sections 5315 and 5316 of Title 5, Government Organization and Employees, and section 3522 of Title 42, The Public Health and Welfare, which amendments have been executed to text.]

§ 11. Establishment of Council of the Inspectors General on Integrity and Efficiency

(a) Establishment and mission.--

(1) Establishment.--There is established as an independent entity within the executive branch the Council of the Inspectors General on Integrity and Efficiency (in this section referred to as the "Council").

(2) Mission.--The mission of the Council shall be to--

(A) address integrity, economy, and effectiveness issues that transcend individual Government agencies; and

(B) increase the professionalism and effectiveness of personnel by developing policies, standards, and approaches to aid in the establishment of a well-trained and highly skilled workforce in the offices of the Inspectors General.

(b) Membership.--

(1) In general.--The Council shall consist of the following members:

(A) All Inspectors General whose offices are established under--

(i) section 2; or

(ii) section 8G.

(B) The Inspectors General of the Office of the Director of National Intelligence and the Central Intelligence Agency.

(C) The Controller of the Office of Federal Financial Management.

(D) A senior level official of the Federal Bureau of Investigation designated by the Director of the Federal Bureau of Investigation.

(E) The Director of the Office of Government Ethics.

(F) The Special Counsel of the Office of Special Counsel.

(G) The Deputy Director of the Office of Personnel Management.

(H) The Deputy Director for Management of the Office of Management and Budget.

(I) The Inspectors General of the Library of Congress, Capitol Police, Government Printing Office, Government Accountability Office, and the Architect of the Capitol.

(2) Chairperson and Executive Chairperson.--

(A) Executive Chairperson.--The Deputy Director for Management of the Office of Management and Budget shall be the Executive Chairperson of the Council.

(B) Chairperson.--The Council shall elect 1 of the Inspectors General referred to in paragraph (1)(A) or (B) to act as Chairperson of the Council. The term of office of the Chairperson shall be 2 years.

(3) Functions of Chairperson and Executive Chairperson.--

(A) Executive Chairperson.--The Executive Chairperson shall--

(i) preside over meetings of the Council;

(ii) provide to the heads of agencies and entities represented on the Council summary reports of the activities of the Council; and

(iii) provide to the Council such information relating to the agencies and entities represented on the Council as assists the Council in performing its functions.

(B) Chairperson.--The Chairperson shall--

(i) convene meetings of the Council--

(I) at least 6 times each year;

(II) monthly to the extent possible; and

(III) more frequently at the discretion of the Chairperson;

(ii) carry out the functions and duties of the Council under subsection (c);

(iii) appoint a Vice Chairperson to assist in carrying out the functions of the Council and act in the absence of the Chairperson, from a category of Inspectors General described in subparagraph (A)(i), (A)(ii), or (B) of paragraph (1), other than the category from which the Chairperson was elected;

(iv) make such payments from funds otherwise available to the Council as may be necessary to carry out the functions of the Council;

(v) select, appoint, and employ personnel as needed to carry out the functions of the Council subject to the provisions of title 5, United States Code, governing appointments in the competitive service, and the provisions of chapter 51 and subchapter III of chapter 53 of such title, relating to classification and General Schedule pay rates;

(vi) to the extent and in such amounts as may be provided in advance by appropriations Acts, made available

from the revolving fund established under subsection (c)(3)(B), or as otherwise provided by law, enter into contracts and other arrangements with public agencies and private persons to carry out the functions and duties of the Council;

(vii) establish, in consultation with the members of the Council, such committees as determined by the Chairperson to be necessary and appropriate for the efficient conduct of Council functions; and

(viii) prepare and transmit a report annually on behalf of the Council to the President on the activities of the Council.

(c) Functions and duties of Council.--

(1) In general.--The Council shall--

(A) continually identify, review, and discuss areas of weakness and vulnerability in Federal programs and operations with respect to fraud, waste, and abuse;

(B) develop plans for coordinated, Governmentwide activities that address these problems and promote economy and efficiency in Federal programs and operations, including interagency and interentity audit, investigation, inspection, and evaluation programs and projects to deal efficiently and effectively with those problems concerning fraud and waste that exceed the capability or jurisdiction of an individual agency or entity;

(C) develop policies that will aid in the maintenance of a corps of well-trained and highly skilled Office of Inspector General personnel;

(D) maintain an Internet website and other electronic systems for the benefit of all Inspectors General, as the Council determines are necessary or desirable;

(E) maintain 1 or more academies as the Council considers desirable for the professional training of auditors, investigators, inspectors, evaluators, and other personnel of the various offices of Inspector General;

(F) submit recommendations of individuals to the appropriate appointing authority for any appointment to an office of Inspector General described under subsection (b)(1)(A) or (B);

(G) make such reports to Congress as the Chairperson determines are necessary or appropriate; and

(H) perform other duties within the authority and jurisdiction of the Council, as appropriate.

(2) Adherence and participation by members.--To the extent permitted under law, and to the extent not inconsistent with standards established by the Comptroller General of the United States for audits of Federal establishments, organizations, programs, activities, and functions, each member of the Council, as appropriate, shall--

(A) adhere to professional standards developed by the Council; and

(B) participate in the plans, programs, and projects of the Council, except that in the case of a member described under subsection (b)(1)(I), the member shall participate only to the extent requested by the member and approved by the Executive Chairperson and Chairperson.

(3) Additional administrative authorities.--

(A) Interagency funding.--Notwithstanding section 1532 of title 31, United States Code, or any other provision of law prohibiting the interagency funding of activities described under subclause (I), (II), or (III) of clause (i), in the performance of the responsibilities, authorities, and duties of the Council--

(i) the Executive Chairperson may authorize the use of interagency funding for--

(I) Governmentwide training of employees of the Offices of the Inspectors General;

(II) the functions of the Integrity Committee of the Council; and

(III) any other authorized purpose determined by the Council; and

(ii) upon the authorization of the Executive Chairperson, any department, agency, or entity of the executive branch which has a member on the Council shall fund or participate in the funding of such activities.

(B) Revolving fund.--

(i) In general.--The Council may--

(I) establish in the Treasury of the United States a revolving fund to be called the Inspectors General Council Fund; or

(II) enter into an arrangement with a department or agency to use an existing revolving fund.

(ii) Amounts in revolving fund.--

(I) In general.--Amounts transferred to the Council under this subsection shall be deposited in the revolving fund described under clause (i)(I) or (II).

(II) Training.--Any remaining unexpended balances appropriated for or otherwise available to the Inspectors General Criminal Investigator Academy and the Inspectors General Auditor Training Institute shall be transferred to the revolving fund described under clause (i)(I) or (II).

(iii) Use of revolving fund.--

(I) In general.--Except as provided under subclause (II), amounts in the revolving fund described under clause (i)(I) or (II) may be used to carry out the functions and duties of the Council under this subsection.

(II) Training.--Amounts transferred into the revolving fund described under clause (i)(I) or (II) may be used for the purpose of maintaining any training academy as determined by the Council.

(iv) Availability of funds.--Amounts in the revolving fund described under clause (i)(I) or (II) shall remain available to the Council without fiscal year limitation.

(C) Superseding provisions.--No provision of law enacted after the date of enactment of this subsection shall be construed to limit or supersede any authority under subparagraph (A) or (B), unless such provision makes

specific reference to the authority in that paragraph.

(4) Existing authorities and responsibilities.--The establishment and operation of the Council shall not affect--

(A) the role of the Department of Justice in law enforcement and litigation;

(B) the authority or responsibilities of any Government agency or entity; and

(C) the authority or responsibilities of individual members of the Council.

(d) Integrity Committee.--

(1) Establishment.--The Council shall have an Integrity Committee, which shall receive, review, and refer for investigation allegations of wrongdoing that are made against Inspectors General and staff members of the various Offices of Inspector General described under paragraph (4)(C).

(2) Membership.--The Integrity Committee shall consist of the following members:

(A) The official of the Federal Bureau of Investigation serving on the Council, who shall serve as Chairperson of the Integrity Committee, and maintain the records of the Committee.

(B) Four Inspectors General described in subparagraph (A) or (B) of subsection (b)(1) appointed by the Chairperson of the Council, representing both establishments and designated Federal entities (as that term is defined in section 8G(a)).

(C) The Special Counsel of the Office of Special Counsel.

(D) The Director of the Office of Government Ethics.

(3) Legal advisor.--The Chief of the Public Integrity Section of the Criminal Division of the Department of Justice, or his designee, shall serve as a legal advisor to the Integrity Committee.

(4) Referral of allegations.--

(A) Requirement.--An Inspector General shall refer to the Integrity Committee any allegation of wrongdoing against a staff member of the office of that Inspector General, if--

(i) review of the substance of the allegation cannot be assigned to an agency of the executive branch with appropriate jurisdiction over the matter; and

(ii) the Inspector General determines that--

(I) an objective internal investigation of the allegation is not feasible; or

(II) an internal investigation of the allegation may appear not to be objective.

(B) Definition.--In this paragraph the term "staff member" means any employee of an Office of Inspector General who--

(i) reports directly to an Inspector General; or

(ii) is designated by an Inspector General under subparagraph (C).

(C) **Designation of staff members.**--Each Inspector General shall annually submit to the Chairperson of the Integrity Committee a designation of positions whose holders are staff members for purposes of subparagraph (B).

(5) **Review of allegations.**--The Integrity Committee shall--

(A) review all allegations of wrongdoing the Integrity Committee receives against an Inspector General, or against a staff member of an Office of Inspector General described under paragraph (4)(C);

(B) refer any allegation of wrongdoing to the agency of the executive branch with appropriate jurisdiction over the matter; and

(C) refer to the Chairperson of the Integrity Committee any allegation of wrongdoing determined by the Integrity Committee under subparagraph (A) to be potentially meritorious that cannot be referred to an agency under subparagraph (B).

(6) **Authority to investigate allegations.**--

(A) **Requirement.**--The Chairperson of the Integrity Committee shall cause a thorough and timely investigation of each allegation referred under paragraph (5)(C) to be conducted in accordance with this paragraph.

(B) **Resources.**--At the request of the Chairperson of the Integrity Committee, the head of each agency or entity represented on the Council--

(i) may provide resources necessary to the Integrity Committee; and

(ii) may detail employees from that agency or entity to the Integrity Committee, subject to the control and direction of the Chairperson, to conduct an investigation under this subsection.

(7) **Procedures for investigations.**--

(A) **Standards applicable.**--Investigations initiated under this subsection shall be conducted in accordance with the most current Quality Standards for Investigations issued by the Council or by its predecessors (the President's Council on Integrity and Efficiency and the Executive Council on Integrity and Efficiency).

(B) **Additional policies and procedures.**--

(i) **Establishment.**--The Integrity Committee, in conjunction with the Chairperson of the Council, shall establish additional policies and procedures necessary to ensure fairness and consistency in--

(I) determining whether to initiate an investigation;

(II) conducting investigations;

(III) reporting the results of an investigation; and

(IV) providing the person who is the subject of an investigation with an opportunity to respond to any Integrity Committee report.

(ii) Submission to Congress.--The Council shall submit a copy of the policies and procedures established under clause (i) to the congressional committees of jurisdiction.

(C) Reports.--

(i) Potentially meritorious allegations.--For allegations described under paragraph (5)(C), the Chairperson of the Integrity Committee shall make a report containing the results of the investigation of the Chairperson and shall provide such report to members of the Integrity Committee.

(ii) Allegations of wrongdoing.--For allegations referred to an agency under paragraph (5)(B), the head of that agency shall make a report containing the results of the investigation and shall provide such report to members of the Integrity Committee.

(8) Assessment and final disposition.--

(A) In general.--With respect to any report received under paragraph (7)(C), the Integrity Committee shall--

(i) assess the report;

(ii) forward the report, with the recommendations of the Integrity Committee, including those on disciplinary action, within 30 days (to the maximum extent practicable) after the completion of the investigation, to the Executive Chairperson of the Council and to the President (in the case of a report relating to an Inspector General of an establishment or any employee of that Inspector General) or the head of a designated Federal entity (in the case of a report relating to an Inspector General of such an entity or any employee of that Inspector General) for resolution; and

(iii) submit to the Committee on Government Oversight and Reform of the House of Representatives, the Committee on Homeland Security and Governmental Affairs of the Senate, and other congressional committees of jurisdiction an executive summary of such report and recommendations within 30 days after the submission of such report to the Executive Chairperson under clause (ii).

(B) Disposition.--The Executive Chairperson of the Council shall report to the Integrity Committee the final disposition of the matter, including what action was taken by the President or agency head.

(9) Annual report.--The Council shall submit to Congress and the President by December 31 of each year a report on the activities of the Integrity Committee during the preceding fiscal year, which shall include the following:

(A) The number of allegations received.

(B) The number of allegations referred to other agencies, including the number of allegations referred for criminal investigation.

(C) The number of allegations referred to the Chairperson of the Integrity Committee for investigation.

(D) The number of allegations closed without referral.

(E) The date each allegation was received and the date each allegation was finally disposed of.

(F) In the case of allegations referred to the Chairperson of the Integrity Committee, a summary of the status of the investigation of the allegations and, in the case of investigations completed during the preceding fiscal year, a summary of the findings of the investigations.

(G) Other matters that the Council considers appropriate.

(10) Requests for more information.--With respect to paragraphs (8) and (9), the Council shall provide more detailed information about specific allegations upon request from any of the following:

(A) The chairperson or ranking member of the Committee on Homeland Security and Governmental Affairs of the Senate.

(B) The chairperson or ranking member of the Committee on Oversight and Government Reform of the House of Representatives.

(C) The chairperson or ranking member of the congressional committees of jurisdiction.

(11) No right or benefit.--This subsection is not intended to create any right or benefit, substantive or procedural, enforceable at law by a person against the United States, its agencies, its officers, or any person.

§ 12. Definitions

As used in this Act--

(1) the term "head of the establishment" means the Secretary of Agriculture, Commerce, Defense, Education, Energy, Health and Human Services, Housing and Urban Development, the Interior, Labor, State, Transportation, Homeland Security, or the Treasury; the Attorney General; the Administrator of the Agency for International Development, Environmental Protection, General Services, National Aeronautics and Space, Small Business, or Veterans' Affairs; the Administrator of the Federal Emergency Management Agency, or the Office of Personnel Management; the Chairman of the Nuclear Regulatory Commission or the Railroad Retirement Board; the Chairperson of the Thrift Depositor Protection Oversight Board; the Chief Executive Officer of the Corporation for National and Community Service; the Administrator of the Community Development Financial Institutions Fund; the chief executive officer of the Resolution Trust Corporation; the Chairperson of the Federal Deposit Insurance Corporation; the Commissioner of Social Security, Social Security Administration; the Director of the Federal Housing Finance Agency; the Board of Directors of the Tennessee Valley Authority; the President of the Export-Import Bank; or the Federal Cochairpersons of the Commissions established under section 15301 of title 40, United States Code; as the case may be;

(2) the term "establishment" means the Department of Agriculture, Commerce, Defense, Education, Energy, Health and Human Services, Housing and Urban Development, the Interior, Justice, Labor, State, Transportation, Homeland Security, or the Treasury; the Agency for International Development, the Community Development Financial Institutions Fund, the Environmental Protection Agency, the Federal Emergency Management Agency, the General Services Administration, the National Aeronautics and Space Administration, the Nuclear Regulatory

Commission, the Office of Personnel Management, the Railroad Retirement Board, the Resolution Trust Corporation, the Federal Deposit Insurance Corporation, the Small Business Administration, the Corporation for National and Community Service, the Veterans' Administration, the Social Security Administration, the Federal Housing Finance Agency, the Tennessee Valley Authority, the Export-Import Bank, or the Commissions established under section 15301 of title 40, United States Code, as the case may be;

(3) the term "Inspector General" means the Inspector General of an establishment;

(4) the term "Office" means the Office of Inspector General of an establishment; and

(5) the term "Federal agency" means an agency as defined in section 552(f) of Title 5 (including an establishment as defined in paragraph (2)), United States Code, but shall not be construed to include the Government Accountability Office.

§ 13. Effective date

The provisions of this Act and the amendments made by this Act [see section 10 of this Act] shall take effect October 1, 1978.