

REPOSITORY LLNL B 361 Rm. B 940A

COLLECTION Institutional Review Board

BOX No. IRB Protocol File
Active Grants-Collabative University of
Washington Ozone Effect on Overall Liver
FOLDER Function

71B072

UNIVERSITY OF WASHINGTON

& UNIVERSITY OF CALIFORNIA, LAWRENCE LIVERMORE LABORATORY

CONSENT FORM FOR INHALATION OF OZONE AND SPECIFIC RADIOACTIVE GASES FOR RESEARCH

Ozone Effects on Overall and Regional Lung Function

Principal Investigator: Robert Frank, M.D. , Department of Environmental Health
University of Washington (206)543-4383

Associates: Jane Koenig, Ph.D., Department of Environmental Health 543-4383
Michael Morgan, Sc.D. Department of Environmental Health 543-4383
Dick Holub, M.S. , Department of Environmental Health 543-4383
Neil Horike, M.S. , Department of Environmental Health 543-4383
Paul Meyer, M.S., Lawrence Livermore Laboratory (415)447-1100
ext. 7226

The purpose of this study is to test the effect of ozone, an important air pollutant, on the pulmonary function of normal, healthy humans.

Persons who have chronic heart disease, lung disease including asthma, or have had any respiratory infection during the past six weeks may not participate. Pregnant women may not participate.

Procedure: The study will involve breathing low concentrations of ozone for two hours. The subject will sit in a small chamber shaped somewhat like a telephone booth and breathe through a mouthpiece. Before the subject enters the chamber, a narrow tube (catheter) will be passed through the nose into the rear of the throat. The subject will then swallow the catheter until the tip lies just above the stomach. The catheter is necessary to estimate intrapleural pressure (the pressure in the space between the lungs and the chest wall) which is used to calculate flow resistance (a measure of the effort required to move air through the airways). Flow resistance will also be measured by a non-invasive method using pressure waves created by a pump (forced pressure oscillatory method). The flow resistance measurements require only quiet breathing on the part of the subject. Other functional measurements will require such simple maneuvers as inhaling and exhaling maximally, exhaling at a given flow rate and occasional breath holding or panting. The radioactive measurements require the subject to inspire a single breath of gas tagged with a low level of radioactivity and hold his breath for 15 to 20 seconds. Following the breathing of the pollutant the subject will come out of the chamber for one hour and thereafter re-enter for another set of measurements lasting 10-15 minutes. The total length of the procedure will be 4-5 hours. Some subject will be asked to exercise moderately on a treadmill for 10-15 minutes while breathing the pollutant.

The risks involved in the study are negligible. Discomforts that may arise are as follows: nasal irritation may be felt when the catheter is first passed; the nose clip may occasionally feel tight; sitting in the chamber may be tedious. The pollutants may cause burning of the throat and anterior chest, or cough, and rarely, difficulty in breathing. Should the symptoms occur, they are likely to be slight and to disappear within minutes or hours. The radioactive gas needed for the measurements will be tested before each procedure and maintained at a level low enough to cause no harmful effects.

INVALID FORM

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If the subject experiences excessive symptoms the experiment will be terminated. A doctor will be present throughout the experiment and will question the subject at least once daily until all symptoms are gone.

The subjects retain the right to withdraw from the study at any point. The subject will be paid \$50 per two-hour exposure session. There are no personal benefits deriving from participation in the study. The rights to withdraw from the test at any time and to withhold information from non-medical persons without additional consent are protected. The subject's welfare is protected by the presence of the physician before and during the test, and by the availability of emergency hospital treatment if the need arises. The subject's identity and all information about him or her are to remain confidential.

Signature of investigator

Date

Subject's statement

I voluntarily consent to participate in this study. I have had an opportunity to ask questions.

Signature of subject

Date

Copies: Subject
File

INVALID FORM

2004685

February 25, 1977

Dr. Robert Frank
Department of Environmental Health 43-34
7463 Health Sciences Building

Re: Application # 7-110-8, "Acute effects on overall and regional lung function."

The Human Subjects Review Committee, Section B, reviewed the above-referenced application for research on February 22, 1977. Approval is contingent upon receipt of the following:

1. A copy of the Radiation Safety Committee (RSC) approval letter.

Revisions in the protocol:

2. Add a section concerning the amount of radiation the person will be exposed to with some gamma measurement. (The RSC can help you with this).
3. Include a statement indicating that these concentrations of ozone may produce changes in pulmonary function, however, these are completely reversed within 24 hours.
4. Indicate in a separate section, that the subject will be wearing a nose clip.

Revisions of current protocol:

5. Paragraph 1, Section 1, change "guilty" to "guiltless."
6. Paragraph 1, Section 2, change "non-invasive" to "non-invasive," and explain the difference in lay terms.
7. Paragraph 2, Section 7, change "structural."
8. Paragraph 3, Section 9, change "In order to obtain maximum... hold a direct breath of gas... and hold his/her breath for 15-20 seconds."
9. Paragraph 4, Section 1, change "use", "ought to be."
10. Paragraph 4, Section 1, change "invasive."

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Application No. 7-315-5
Human Subjects Review Committee
February 25, 1977

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Para 2 of application

13. Paragraph 1, sentence 2, insert after "and", "hereafter."

Please send one copy of the Radiation Safety Committee approval letter and copies of the revised consent form to Ms. Susanna Keller, Human Subjects Office, 1 Administration MD-22. Inquiries may be addressed to Ms. Keller at 3-7657. When final action has been taken you will be sent an approved copy of your application.

Sincerely,

Marina L. Patrick, Dr. P.H.
Chairman, Section B
Human Subjects Review Committee

MLP:lek

cc: Dr. John T. Wilson, Jr.

UNIVERSITY OF WASHINGTON

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The purpose of this study is to test the effect of ozone, an important air pollutant, on the pulmonary (lung) function of normal, healthy humans.

Persons who have chronic heart disease, lung disease including asthma, or have had any respiratory infection during the past six weeks may not participate. Pregnant women may not participate.

Procedure: The study will involve breathing low concentrations of ozone for two hours. The subject will sit in a small chamber shaped somewhat like a telephone booth and breathe through a mouthpiece. Before the subject enters the chamber, a narrow tube (catheter) will be passed through the nose into the rear of the throat. The subject will then swallow the catheter until the tip lies just above the stomach. A noseclip will be used to hold the catheter in place and to prevent nose breathing. The catheter is necessary to estimate intrapleural pressure (the pressure in the space between the lungs and the chest wall) which is used to calculate flow resistance (a measure of the effort required to move air through the airways). Flow resistance will also be measured by a non-invasive method using pressure waves created by a pump (forced pressure oscillatory method). The flow resistance measures require only quiet breathing on the part of the subject. Other measurements will require such simple maneuvers as inhaling and exhaling maximally, exhaling at a given flow rate and occasional breath holding or panting. In order to obtain the radioactive measurements the subject will inhale a single breath of gas tagged with a low level of radioactivity ($^{13}\text{N}_2$ or C^{15}O_2 , both positron emitters) and hold his/her breath for 15 to 20 seconds. Following the breathing of the pollutant the subject will come out of the chamber for one hour and thereafter re-enter for another set of measurements lasting 10-15 minutes. The total length of the procedure will be 4-5 hours. Some subject will be asked to exercise moderately on a treadmill for 10-15 minutes while breathing the pollutant.

The risks involved in the study are thought to be negligible. * add Discomforts that may arise are as follows: nasal irritation may be felt when the catheter is first passed; the nose clip may occasionally feel tight; sitting in the chamber may be tedious. The ozone may cause burning of the throat and chest, or cough, and rarely, difficulty in breathing. Should the symptoms occur, they are likely to be slight and to disappear within minutes or hours. The total radiation exposure for the complete experiment (12 radioactive tests) will be approximately 30 mrad to the lungs, the acceptable dose limit to the lungs is 500 mrad per year. A normal chest x-ray will result in approximately 200 mrad to the skin.

Adel
* The low concentrations of ozone may produce changes in pulmonary function not noticeable to the subject, however, these are completely reversed within 24 hours.

2004688

APPROVED FORM

If the subject experiences excessive symptoms the experiment will be terminated. A doctor will be present throughout the experiment and thereafter will question the subject at least once daily until all symptoms are gone.

The subjects retain the right to withdraw from the study at any point. The subject will be paid \$50 per two-hour exposure session. There are no personal benefits deriving from participation in the study. The rights to withdraw from the test at any time and to withhold information from non-medical persons without additional consent are protected. The subject's welfare is protected by the presence of the physician before and during the test, and by the availability of emergency hospital treatment if the need arises. The subject's identity and all information about him or her are to remain confidential.

Signature of investigator

Date

Subject's statement

I voluntarily consent to participate in this study. I have had an opportunity to ask questions.

Signature of subject

Date

COPIES: Subject
File

2004689

UNIVERSITY OF WASHINGTON

Human Subjects Office

February 2, 1977

To: Investigators using human subjects in University activities
From: Diana McCann, Director *D. McCann*
Subject: Insurance for unanticipated adverse effects

Since July 1, 1972, the University has carried insurance to cover unanticipated adverse effects occurring to human subjects as the result of participation in activities sponsored by the University of Washington. The insurance provides benefits similar to those available under the Washington Industrial Insurance Act (workmen's compensation); Aetna Insurance Company is the current insurer. This policy supplements the University's liability and malpractice insurance coverage.

Unanticipated adverse effects should be reported by means of the "Use of Human Subjects - Adverse Effect Report" form. *This form is provided upon request after an unanticipated adverse effect has occurred. In the event of such an occurrence, please call me at telephone 543-7853 for further details.

DM:km

*Not to be confused with the Human Subjects Review Committee Application form.

2004690

UNIVERSITY OF WASHINGTON

APPROVED
MAR 17 1977

Human Subjects Review Committee Application

7-216-B

Date February 2, 1977

Please type; use supplemental sheets, as needed. Submit 15 copies, including a signature copy, to Research Services, AG-10. Each copy should have all relevant materials, e.g., consent form(s), questionnaires, other, unless otherwise specified in this application form.

- | | <u>Name and position</u> | <u>Department/Division</u> | <u>Mail Stop</u> | <u>Telephone</u> |
|-------------------------|--------------------------|---------------------------------------|------------------|------------------|
| I. Investigator: | Robert Frank, Professor | Environmental Health | SC-34 | 543-4383 |
| Associates: (U. of W.): | Michael Morgan | Neil Horike | | |
| | Dick Holub | (Lawrence Livermore Labs): Paul Meyer | | |
| | Jane Koenig | | | |
- II. Names of other persons responsible for performing or supervising procedures.

II. Title of proposed activity.

Ozone Effects on Overall and Regional Lung Function

IV. Beginning date of proposed activity. 7/1/77

- V. Is this activity related to a grant or contract? Yes X No If yes, complete A-J.
- A. Is it related to a training grant? Yes No X If no, ATTACH ONE COPY (without budget).
- B. Is it related to a fellowship? Yes No X
- C. Has proposal been submitted? Yes X No
- D. Has award been made? Yes X No
- E. Name of Principal Investigator shown (or to be shown) on proposal: Robert Frank
- F. Name of agency to which proposal was (or will be) submitted: NIH
- G. If continuation (or already awarded), what is the agency's grant or contract number?
S R01 HL 18925-02
- H. Title of proposal shown (or to be shown) on GC-1 form:
- I. Inclusive dates of grant or contract:
From 7/1/75, through 6/30/78
- J. Will activity be performed if funding is not received? Yes X No

VI. Recommendations and action:

Date Approve Disapprove

- A. Department Chairman John T. Wilson, Jr. 3/3/77
Typed name, plus signature
- B. Faculty Sponsor
(for student) Typed name, plus signature
- C. Human Subjects Review Devin Patrick MAR 17 1977 X
Committee Chairman's signature

Subject to the following conditions: the addition as shown on page one

of the approved consent form

Period of approval from March 17, 1977, through March 16, 1978.

Valid only as long as approved procedures are followed.

ii. Checklist to be completed by investigator:

Yes No

- A. Will another organization or agency be involved (Veterans Administration Hospital, Department of Social and Health Services, or others)? x
 Name of other organization or agency:
- B. Will materials with potential radiation risk be used, e.g., X-rays, radio-isotopes? If yes, x
 1. Status of review by Radiation Safety Committee (RSC). (If approved, ATTACH ONE COPY of approval.)
 2. Title of application submitted to RSC.
- C. Will an investigational new drug (IND) be used? x
 If yes, name, proposed dosage, status with Food and Drug Administration, and IND number. ENCLOSE ONE COPY of available toxicity data.
- D. Will other drugs be used? x
 If yes, names and dosages.
- E. Should this activity be covered by the adverse effects' insurance? x
- F. Will a written consent form(s) be used? (Required in most cases.) x
 1. If no, explain why a written consent form will not be used.
 2. If no, is a statement attached describing what participants will be told?
 Participants must be informed of all elements of VII.G. below.
- G. Does (Do) the consent form(s) include: (Page 4 provides a sample format--tear off, do not submit to Research Services). x
 "University of Washington" heading? x
 Name, position, department, and telephone number of investigator? x
 Date? x
 Copy for subject? x
 Signature and date lines to be completed by subject (and legal guardian, if subject is a minor or is legally incompetent), and investigator? x
 The following elements of consent expressed in lay terms: x
 1. Purpose--benefits to be expected or knowledge hoped to be gained?
 2. Procedures to be followed, including identification of those which will be performed only for the purposes of this activity, and time involved? x
 3. Nature and amount of risk, or substantial stress or discomfort involved? x
 4. Appropriate alternate procedures that might be advantageous or available to subject? (Show "N/A" (not applicable) when there are none.) N/A
 5. Costs the subject may immediately or ultimately be forced to bear and what reimbursement of costs or other compensation the subject will receive as the result of participation in this activity? N/A
 6. Voluntary nature of participation and freedom to withdraw at any point without penalty? x
 7. Opportunity to ask questions before consenting? x
 8. Assurance that subject's identity will remain confidential? x

I. Subjects.

- A. Approximate number and ages: Normal, patient, either. 16 health subjects per year; ages 20 to 65
- B. Criteria for selection and exclusion. Healthy subjects with no history or X-ray of chronic or recent cardiopulmonary disease. Minors and pregnant women will be excluded.
- C. Source of subjects (including patients), and how they will be approached. Healthy subjects announcements posted on bulletin boards at UC, San Francisco and Lawrence Livermore Labs, Livermore, California
- D. Will subjects be paid or otherwise compensated? If so, what amount? and what is the reason for payment?

Healthy subjects will be compensated \$50 for the time and travel involved.

- E. Location where procedures will be carried out.

Linear Accelerator Bldg., #194, Lawrence Livermore Labs, Livermore, California

X. Confidentiality and anonymity.

- A. Steps to insure that participation by subjects will be kept confidential. Anonymity of documents and data

- B. Provisions to insure anonymity of documents and data.

Data will be identified by number and available to authorized personnel only

- C. Provision for controls over access to documents and data.

Data and documents will be stored in a locked file

X. What publications might be helpful to the committee in consideration of this application? (Answer only if these might expedite review.)

I. Outline of activity (circle OPTION you will use in responding):

FIRST OPTION: Provide answers in spaces following A-F below (add sheets, when needed).

SECOND OPTION: Provide answers in attached summary statement (reference, if over one page)

- A. Background or rationale for this activity.

To determine the respiratory effects of low levels of ozone in healthy adults at rest and during exercise.

- B. Objectives.

See add. sheet

- C. Procedures involved.

(Which of these will be performed only for the purposes of this activity, e.g., volume of blood, size of biopsy, questionnaire, name of psychological test?)

See add. sheet

- D. Identify alternate procedures, if any, not proposed for this activity that might be advantageous to the subject. none

- E. If any deception (withholding complete information) is required for the validity of this activity, explain why this is necessary and attach debriefing statement.

N/A

5. Nature and amount of risk (include side effects), or substantial stress or discomfort involved.

See add. sheet

1. Follow-up planned for procedures and possible adverse effects. If symptoms occur and persist, daily interview by phone will be made until all symptoms have abated

2. Arrangements for financial responsibility for adverse effects, To be assumed by ~~the University of California~~ University of Washington

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XI. B. Objectives

To study the effects of acute low level exposure to ozone (< 0.5 ppm) on overall and regional lung function

C. Procedures Involved

Non radioactive measurements (overall function)

The subject will be seated, at rest in a conventional body plethysmograph breathing quietly. For the measurements of pulmonary compliance and flow resistance, a thin balloon tipped esophageal catheter is to be swallowed so that the tip lies in the lower third of the esophagus. Some subjects may experience slight discomfort while the catheter passes through the posterior pharynx; otherwise the procedure is harmless. A nose clip is worn to anchor the catheter in place. The catheter is used to measure the pressure gradient between the esophagus (analogous to the pleural surface) and the mouth. The other two parameters required to calculate compliance and flow-resistance, the tidal volume and the rate of flow, will be measured with a flow meter attached to a conventional mouthpiece. Each set of measurements requires 5-10 minutes. Between measurements, the subject will breathe the ozone through a mask.

Following the end of exposure, all measurements will be repeated until the control values are re-established.

Exercise will be achieved by working on a treadmill at about 3 mph on a 5% grade for 10-15 minutes. The periods of exercise may be repeated for a total of four 10-15 minute sessions interspersed with quiet breathing (total exposure = 2 hours). Ventilation and heart rate will be measured.

Radioactive measurements (regional function) based on the technique of West et al.

The subject will be standing at rest between the two heads of the Anger Position Camera. A single breath of $^{13}\text{N}_2$ or C^{15}O_2 will be inspired from a plastic bag and the subject will hold his breath for 15 to 20 seconds. The Anger camera will record the distribution of the radioactive gas.

- F. We intend to administer concentrations of ozone (0.2 - 0.5 ppm) that have been employed in a number of previous investigations on healthy volunteers (2-7). These concentrations of ozone may produce changes in pulmonary function which are completely reversed within 24 hours and which are not perceived by the subject (the subject is not aware of the slight increase in pulmonary flow resistance, slight decrease in maximal forced expiratory flow rates, or slight decrease in diffusing capacity that may occur. is not unusual for subjects to experience throat irritation, tickling sensation in the throat, and cough at these concentrations. Such symptoms also regress within 24 hours. There has never been a report of unusual

distress or hospitalization arising from such exposures. While exercise tends to increase the functional effects and symptoms, there are no reports of untoward reactions associated with this procedure. Concentrations of 0.2 - 0.5 ppm of O₃ have been reached on numerous occasions in the Los Angeles basin and are exceeded in a number of occupational and industrial settings.

The radioactivity tagged gas ¹³N₂ and C¹⁵O₂ will be produced using the techniques of West et al. (2 and 9). Each bag of gas will be tested for any radioactive and non radioactive contaminants by personnel from the Hazards Control Section, Lawrence Livermore Laboratory, before administration to the subject.

REFERENCES

1. West, J.B.: Pulmonary function studies with O^{15} , C^{11} and N^{13} . In Dynamic Clinical Studies with Radioisotopes. U. S. Atomic Energy Commission. Oak Ridge, 1964, pp. 213-236.
2. Young, W.A.; Shaw, D.B.; and Bates, D.V.: Effect of low concentrations of ozone on pulmonary function in man. *J. Appl. Physiol.* 19, 765-768, 1964.
3. Goldsmith, J.R., and Nadel, J.A.: Experimental exposure of human subjects to ozone. *J. Air Pollution Control Assoc.* 19, 329-330, 1969.
4. Bates, D.V.; Bell, G.M.; Burnham, C.D.; Hazucha, M; Mantha, J.; Pengelly, L.D.; and Silverman, F.: Short-term effects of ozone on the lung. *J. Appl. Physiol.* 32:176-181. February 1972.
5. Hazucha, Milan, M.D.; Silverman, Frances, MSc; Parent, Claude, BSpSc; Field, Stephen, BSc; and Bates, David V., M.D.: Pulmonary Function in Man after Short-Term Exposure to Ozone, Montreal, Canada. Sept., 1973. 27:183-188.
6. Kerr, H.D.; Kulle, T.J.; McIlhany, M.L.; and Swidersky, P.: Effects of Ozone on Pulmonary Function in Normal Subjects, an Environmental-Chamber Study. *Amer. Review of Respiratory Disease*, 3:763-773, 1975.
7. Folinsbee, L.J.; Silverman, F.; and Shephard, R.J.: Exercise responses following ozone exposure. *J. of Appl. Physiol.*; Toronto, Ontario, Canada. 38 no. 6:996-1001; June, 1975.
8. DeLucia, A.J., and Adams, W.C.: Effects of O_3 Inhalation During Exercise on Pulmonary Function and Blood Biochemistry. Submitted to *J. Appl. Physiol.*, 1976.
9. Buckingham, P.D., and Forse, G.R.: The preparation and processing of radioactive gases for clinical use. *Int. J. of Appl. Rad. and Isotopes.* 14:439-445, 1963.