

APPLICATION FOR AUTHORIZATION TO USE

RADIATION WITH HUMAN SUBJECTS

Submitted Feb 3 1977 Form RSC 30(76)

DOCKET NUMBER

Applicant

Provide Identical Information From Form UW 13-11 For First Section

I. Investigator Department Mail Stop Telephone
Robert Frank, Professor Environmental Health SC-34 543-4383

U. of W: Michael Morgan, Dick Holub, Jane Koenig, Neil Horike 718074

II. Names of Persons Responsible for Procedures (other than I.)

Paul Meyer, University of California, Lawrence Livermore Laboratory, Livermore, California (415) 447-1100 ext. 7226

III. Title of Proposed Activity

Ozone Effects on Overall and Regional Lung Function

IV. Beginning Date of Proposed Activity 7/1/77

VIII. Subjects (attach copy of response to 13-11)

XI. Outline of Activity (attach copy of response to 13-11)

Attach Copy of Consent Form

If radiation source is not a standard clinical facility an Application for Authorization to Use Radiation will be required in addition to the application (Form RSC 10(76)).

The applicant should attach information relative to each point below. Please use the same numbers and subtitles. For more complete instruction refer to Guidelines for Application for Authorization to Use Radiation with Human Subjects

- 1. Education and Training (Form RSC 20(76))
2. Description of Research Project
3. Description of Subjects
4. Benefit to Subjects
5. Limits of Study
6. Basis for Selecting (and Rejecting) Potential Subjects.
7. Radiation Protection Measures for the Subject
8. Radiation Dosimetry
9. Summary of Risk to Subject
10. Consultation with Radiation Specialist
11. Report of Progress or Completion of Project

REPOSITORY L1111 B361 Rm89408
COLLECTION Institutional Review Board
BOX No. IRB Protocol File
FOLDER Active Grants-Collaborative
University of Washington Ozone
Effect on Overall Lung
Function

Other Attachments (list).

References:(1) Meyer, P.; Behrin, E; Frank, R.; Holub, R.; and McJilton, C.E. Biomedical Application of Shortlived Positron Emitting Isotopes. Preprint: 1-3. February 1975

(2) Meyer, P. Ozone-Tagging for Biomedical Purposes, Lawrence Livermore Laboratory, 7-20-72. This application and attachments are provided to the Radiation Safety Committee for approval.

Department Chairman

Applicant

[Signature]

Robert Frank

2004698

Date 1/25/77

II. 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

IX. 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.)

VI. 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

- F. 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 Univ. of Calif.

2004701

.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 O_3 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 $^{13}N_2$ and $C^{15}O_2$ 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.

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-evasive 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 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.

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

STATEMENT OF TRAINING AND EXPERIENCE
IN RADIATION WORK

PRIVACY ACT MATERIAL REMOVED

Form RSC 20(76)

Name Paul Meyer Social Security Number _____
 Title/Position Physicist
 Address Lawrence Livermore Laboratory, Livermore, CA 94550

TYPE OF TRAINING	FORMAL COURSE		ON THE JOB		WHERE	DURATION
	yes	no	yes	no		
a) Principles and Practices of Radiation Protection			X		LLL, Livermore	10 years
b) Radiation Measurements Monitoring Techniques and Instruments	X		X		LLL, Livermore	10 years
c) Mathematical and Calculations Basic to use and Measurement of Radiation	X		X			
d) Biological Effects of Radiation	X				LLL, Livermore	

FORMAL COURSES Please describe by title and course content each formal course indicated by "yes" in the first column. (For additional space use reverse side.)

Courses providing the type of training listed under (b) and (c) above where part of the curriculum required for my Master of Science in Physics degree granted by the University of Washington in 1960.

(d) Biological effects of ionizing radiation (CE 4300): A survey course in radiation biology designed to provide a basic understanding of radiation effects on biological systems. Emphasis was on biological phenomena with special reference to human dose-effect relationships.

EXPERIENCE Describe actual use of radiation either as part of a formal course or as laboratory employee. Indicate type of radiation or radioactive material, amounts, uses, duration of work and your involvement and where experience occurred. (For additional space use reverse side.) As an experimental physicist at the Linear Electron Accelerator at LLL, I have been producing radioisotopes like ^{11}C , ^{13}N , ^{15}O and other gases to be used in physics experiments as well as in biomedical applications with live dogs over the past four years at Livermore.

HUMAN USE Describe your experience in administration of radiation to humans that qualifies you for work described in the application. Provide name of preceptor physicians who supervised this training. (Use reverse side for additional space.)

2004707

Signed Paul Meyer

Date Jan. 6, 1977

3. Description of Subjects: Healthy Subjects, male or female, 20 to 65 years in age.
4. Benefit to Subjects: Participation in experiment designed to measure the effects of a common air pollutant at levels which are currently found in many of our larger cities and urban areas.
5. Limits of Study: 16 subjects for one year.
6. Basis for Selecting (and Rejecting) Potential Subjects:
Healthy subjects with no history or X-ray of chronic or recent cardiopulmonary disease. Minors and pregnant women will be excluded.

7-10 See attached memo to Paul Meyer

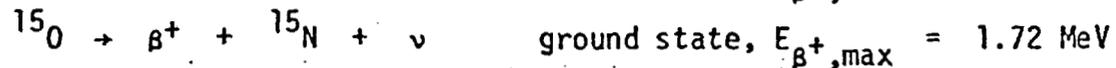
December 13, 1976

TO: Paul Meyer

FROM: M. S. Singh/T. R. Crites

SUBJECT: Estimates of Dose to the Lungs From ^{13}N and ^{15}O Due to Inhalation

Radionuclides ^{13}N and ^{15}O are both positron emitters and decay into the ground state of ^{13}C and ^{15}N , respectively, as follows:



As the positron moves through matter it loses kinetic energy and finally combines with an electron to form a positronium atom which decays into two 0.51 MeV gammas.

Dose delivered to the lungs is thus primarily from positrons and 0.51 MeV gammas.

The effective absorbed energy from positron emitters can be estimated to be¹

$$E = 0.33 E_{\beta^+, \text{max}} f \left(1 + \frac{E_{\beta^+, \text{max}}^{0.5}}{4} \right) + 2(0.51) f_a f$$

where f_a is the fraction of 0.51 MeV gamma energy absorbed in the lungs and f is the number of positrons per disintegration, which is equal to one in our case.

The absorbed fraction of 0.51 MeV gamma energy in the lungs (mass of lungs is approximately 600 g, excluding arterial and venous blood) is 3.05%.² Therefore, the effective absorbed energy in lungs from positron emitters becomes

$$\begin{aligned} E &= 0.33 E_{\beta^+, \text{max}} \left(1 + \frac{E_{\beta^+, \text{max}}^{0.5}}{4} \right) + 0.031 \\ &= 0.531 \text{ MeV for } ^{13}\text{N}, \text{ and } \parallel \quad (E_{\text{max}}^{13}\text{N} = 1.20 \text{ MeV}) \\ &= 0.785 \text{ MeV for } ^{15}\text{O}. \quad \parallel \quad (E_{\text{max}}^{15}\text{O} = 1.74 \text{ MeV}) \end{aligned}$$



Dose rate per mCi maintained in the lungs is

$$D_R = \frac{E(\text{MeV/d})}{600 \text{ g}} \times \frac{1.6 \times 10^{-6} \text{ erg}}{\text{g}} \times \frac{\text{rad-g}}{100 \text{ erg}} \times \frac{3.7 \times 10^7 \text{ d/s}}{\text{mCi}}$$

$$= E \times 9.87 \times 10^{-4} \frac{\text{rad/s}}{\text{mCi}}$$

For a one time exposure with radionuclides retained in the lungs, the absorbed dose is simply

$$D = D_R \times \frac{1 - e^{-\lambda t}}{\lambda} \frac{\text{rad}}{\text{mCi}}$$

where λ is the effective decay constant and t is the residence time for nuclides in the lungs.

The integrated dose per mCi for one breath held for time, t_h , and then normal breathing resumed is

$$D_I = D_R \times \left(\frac{1 - e^{-\lambda_h t_h}}{\lambda_h} + \frac{e^{-\lambda_h t_h}}{\lambda_h + \lambda_c} \right)$$

where λ_h is the effective decay constant while holding breath and λ_c is the clearance decay constant once breathing is resumed.

Table 1 summarizes the calculated dose rates and integrated dose equivalents delivered to the lungs for various breath hold-up times.

Table 1. Calculated dose to the lungs due to inhalation of ^{13}N and ^{15}O .

Radio-nuclide	$T_{1/2}$ (s)	λ_h (s^{-1})	λ_c (s^{-1})	D_R $\frac{\text{rad-s}^{-1}}{\text{mCi}^{-1}}$	D $\frac{\text{rad-mCi}^{-1}}{\text{mCi}^{-1}}$	t_h (s)	D_I $\frac{\text{rad-mCi}^{-1}}{\text{mCi}^{-1}}$
^{13}N	600	1.16×10^{-3}	2.31×10^{-1}	5.24×10^{-4}	4.52×10^{-1}	15	9.98×10^{-3}
						30	1.75×10^{-2}
						45	2.51×10^{-2}
						60	3.25×10^{-2}
^{15}O	120	5.78×10^{-3}	2.31×10^{-1}	7.75×10^{-4}	1.34×10^{-1}	15	1.42×10^{-2}
						30	2.42×10^{-2}
						45	3.33×10^{-2}
						60	4.17×10^{-2}

A review of the literature reveals a few additional calculational methods producing about the same estimate.

ICRP #13, Protection of the Patient in Radionuclide Investigations, reports the total dose to the lungs due to a single breath of 150 to be 16 mrad/mCi/l and 3.6 mrad/mCi/l to the gonads. Holding the gas in the lungs for 15 seconds will increase this dose less than a factor of two. They also report the total dose from breathing 1 mCi/l ^{13}N for 1 minute to be 68 mrad to the lungs and less than 1 mrad to the gonads. The designed experiment will result in doses less than this.

Publications of the Medical Internal Radiation Dose Committee (MIRD) pamphlets list 3.06×10^{-4} rad mCi $^{-1}$ s $^{-1}$ due to 150 , and 4.4×10^{-4} rad mCi $^{-1}$ s $^{-1}$ due to ^{13}N . The difference between the dose rate, D_R , that appears in Table 1 and this one is attributable to the basic assumption made in considering the mass of the lungs. In our case we have excluded the arterial and venous blood, whereas MIRD Committee included this mass in their calculations. Other than this, the results are agreeable.

An additional reference by W. H. Blahd in Nuclear Medicine indicates a procedure of the type proposed will result in 35 mrad/mCi ^{13}N . We feel this is a somewhat conservative estimate.

Table 2 lists the current acceptable dose limits for various conditions.

Table 2. Acceptable dose limits to the lungs.

<u>Condition</u>	<u>Dose</u>
Occupational	15 rem/y (5 rem/qtr)*
Individual	0.5 rem/y*
Population	0.17 rem/y*
Clinical	4000 rad**

* Current NCRP dose limits.

** 4000 rads is the minimal clinical tolerance dose to lungs which results in no more than 5% severe complications, i.e., radiation pneumonitis and fibrosis, within five years following treatment.

M S Singh

M. S. Singh
Health Physics Group
Hazards Control Department

T. R. Crites

T. R. Crites, Leader
Special Projects Division
Hazards Control Department

MSS:TRC:gw
cc: R. Alvarez
D. Myers
J. Powell

2004711

References

1. Report of Committee II on Permissible Dose for Internal Radiation, ICRP, Pub. 2 (Pergamon Press, Oxford, 1960).
2. Report of the Task Group on Reference Man, ICRP, Pub. 23 (Pergamon Press, Oxford, 1975).

a. *Name, Title, Department of Applicant*
 Robert Frank, Professor
 Department of Environmental Health
 School of Public Health & Community Medicine

1(b). *Building (s) and Room (s) For Use*
 Experiments will be performed at
 University of California,
 Lawrence Livermore Laboratory,
 Livermore, Calif.
 Linear Accelerator Bldg. #294
 (415) 457-1100, ext. 7226

a). *Mailing address and Office Address*
 SC-34, F-561F, Health Sciences Bldg.

2(b). *Telephone*
 543-4383

Other Radiation Used by Applicant

none

**Individual Users (Name and Title)*

Paul Meyer, Physicist, Lawrence Livermore Laboratory

a). **Local Radiation Safety Agent*
 Hazards Control, LLL

5(b). *Emergency Phone Numbers*

RADIATION SOURCE (S)

6(a). Radionuclide	6(b). Chemical/Physical Form	6(c). Maximum * Activity mCi/liter	6(d). Dose/exposure (30 sec)
¹³ N	Gaseous	.072 mCi/liter	1.34 mrad/liter 30 sec(30%)
¹⁵ O	"	.0037 mCi/liter	.091 mrad/liter 30 sec(30%)

*Based on calibration measurements by LLL-Hazards Control personnel.

(e). *Describe other radiation sources (e.g., X-ray machine, neutron generator)*

(f). *List Title(s) of Projects (Include grant/contract numbers).*

Ozone Effects on Overall and Regional Lung Function, S R01 HL 18925-02

Training and Experience Records for each individual should be submitted if not on file with the Radiation Safety Office. Use Form RSC 20(76).

APPLICATION FOR AUTHORIZATION
TO USE RADIATION

Docket Number _____
Applicant _____

Form RSC 10(76)

8. RADIATION INSTRUMENTS

<u>TYPE</u> <u>Manufacturer & Model</u>	<u>DETECTS</u> <u>α B (γ) n</u>	<u>SENSITIVITY</u>	<u>WINDOW</u> <u>mg/cm²</u>	<u>SCOPE TYPE</u> <u>(e.g., G.M., NaI)</u>	<u>LOCATION</u> <u>Room & Bldg.</u>
Anger Positron Camera				NaI	Livermore

9. SPECIAL FACILITIES. Describe special facilities and equipment (e.g., fume hood, shielding).

10. SPECIAL PRACTICES. Describe special lab radiation safety practices (e.g., monitoring, bioassay).

Continuous monitoring of experimental area.

11. WASTE DISPOSAL. Describe waste disposal program. Estimate quantities per month of liquid, solid, perishables.

The applicant accepts full responsibility for the safe use of radiation described in this application. The applicant further agrees to conform to Rules and Regulations for Radiation Protection, WAC 402, U of W Radioactive Material License Conditions, and U of W Radiation Safety Committee policies.

Department Chairman

Applicant

Date _____

Date _____

2004714

REPRINTED FROM NBS SP 425 Volumes I and II

Nuclear Cross Sections and Technology

Proceedings of a Conference
Washington, D.C.
March 3-7, 1975

Edited by

R. A. Schrack and C. D. Bowman

Center for Radiation Research
National Bureau of Standards
Washington, D.C. 20234



U.S. DEPARTMENT OF COMMERCE, Rogers C. B. Morton, *Secretary*
NATIONAL BUREAU OF STANDARDS, Ernest Ambler, *Acting Director*

Issued October 1975

2004715

BIOMEDICAL APPLICATION OF SHORTLIVED POSITRON EMITTING ISOTOPES†

P. Meyer and E. Behrin
Lawrence Livermore Laboratory
Livermore, California 94550

R. Frank, R. Holub and C. E. McJilton
University of Washington
Seattle, Washington 98105

Radioactive nitrogen, oxygen and ozone have been used for dynamic lung-function studies on live dogs with an Anger positron camera. In particular an attempt was made to determine the feasibility of this method to study early functional changes caused by ozone.

(Radioactive tracers; Anger positron camera, lung function)

Introduction

Ozone has been identified as a significant component of ambient air pollution where atmospheric photochemical activity occurs. The importance of ozone,¹ (O_3), as a toxicant has been investigated and several of its effects have been defined, although the mechanism is still uncertain.²

The results of this research have led, in part, to an interest in where the ozone is taken up in the respiratory system. At present the distribution of the ozone-uptake throughout the airways is unknown.

By tagging ozone with an ^{15}O isotope, actual sites of O_3 -uptake may be discovered.

More information as to the effects of ozone on the lung function can possibly be obtained by the use of ^{13}N tracers in a breathing gas. Nitrogen is not usually soluble in the blood, stays in the lungs until recirculated and, labeled with a ^{13}N tracer its distribution can provide a useful image of a lung. Using radioactive Nitrogen periodically, functional changes in the respiratory system due to, for instance, ozone may perhaps be detected early.

The ^{13}N and ^{15}O isotopes were produced by bremsstrahlung from the 100 MeV Livermore Electron Accelerator (Linac) via $^{14}N(\gamma, n) ^{13}N$ and $^{16}O(\gamma, n) ^{15}O$.^{3,4} Thresholds for these reactions are 10.4 MeV (^{14}N) and 15.7 MeV (^{16}O). Both isotopes decay by positron emission with half lives of 10 min. and 2 min., respectively. After irradiation, the tracer gas was pumped to the anesthetized, mechanically ventilated animal which was placed between the two detector crystals of the positron camera. The camera detects the two .51 MeV annihilation gamma rays in coincidence and stores the information in the memory of an on-line PDP-15 computer. Data transfer from the computer to a magnetic drum is initiated breath by breath so that, in principle, single breath studies can be made, the quality depending primarily on the level of activity of the gas.

Radioactive Gas Production

A stainless steel bottle of 2 liters volume, located downstream behind the tantalum bremsstrahlung target of the Linac, was pressurized with pure O_2 and irradiated with γ -rays of about 30 MeV end-point energy having a typical bremsstrahlung spectrum. To minimize the production of ^{11}C from the reaction $^{16}O(\gamma, n) ^{11}C$ it was desirable to keep the maximum γ -ray energy near the 26.5 MeV threshold for this reaction. After an irradiation time of about 2 half-lives (4 minutes) the exposed gas, now a mixture of

O_2 , $^{*}O_2$, O_3 and $^{*}O_3$, (the astericks refer to molecules with an ^{15}O atom) has nearly reached saturation activity. Since there is no way to differentiate between the decay of $^{*}O_2$ or $^{*}O_3$ it was necessary to eliminate the activated oxygen. This was accomplished by passing the mixture through an ozone trap of silica gel at dry-ice temperature ($-78^{\circ}C$). After collecting sufficient amounts of ozone, the trap was flushed with clean oxygen to remove all $^{*}O_2$, then heated to release the ozone which then was mixed with air to the desired concentration, 1ppm or 5ppm, for an animal exposure.

Similarly, $^{*}N_2$ was produced by using N_2 as a target gas to which clean oxygen was added after irradiation.

Anger Positron Camera⁵

The camera's operation depends on detecting, in coincidence, the two back-to-back gamma rays from a positron-electron annihilation and thus defining a line between the two detector crystals along which the event took place. Many events allow then, in principle to determine the point or points of intercept and thus the location of the source of activity.

The Livermore camera⁶ consists of two identical detector heads, each with 37 photomultiplier tubes mounted on a 40 cm dia. NaI-crystal of 1.25 cm thickness (Figs. 1a,b). Each head derives position information, i.e. where on the X-tal the gamma rays hit, from a precision-capacitor network coupled with the P.M.T.-outputs. These outputs are sampled, digitized and stored on a high-speed drum by the PDP-15. The camera heads can also be used independently as scintillators with position sensitivity. Maximum count-rate capability is 2×10^5 positron events per second.

Annihilation pairs are ordered into a 100×100 matrix permitting, in principle, a spatial resolution of about .3 cm. In practice, the camera's point-source resolution is only about 1.5 cm. However, the extrapolated range⁷ of the ^{15}O -positron ($E_{max} = 1.74$ MeV) in lung tissue of density $\bar{\rho} = .23g/cc$ is about 3.5 cm and the resolution is thus limited by this fact. For the ^{13}N -positron the max. range is somewhat shorter.

During collection, data is displayed on an oscilloscope with four brightness levels controlled by the PDP-15. Hard-data-output is available in graphical form as well as in a digital map, giving the number of annihilation events versus matrix location. Corrections for decreased counting efficiency near the edges of the detectors can be applied as a function of

camera radius. All data shown below has been corrected accordingly.

Discussion

The experiments described here were performed on an 18 lb. beagle resting on its back between the two detector crystals of the camera so that the lung was centrally located. During an exposure, the dog was forced to breathe from a reservoir filled with air and tagged nitrogen or ozone. A teflon lined pump (to minimize decomposition of the ozone) served to control the breathing rate. The procedure was to image the lung by first administering a mixture of 80% $^{15}\text{O}_2$ and 20% $^{14}\text{O}_2$ (Fig. 2). The activated nitrogen is well suited for this purpose since it does not enter significantly into the pulmonary bloodstream, hence remains in the airways until ventilated with clean air. This ventilation was followed by an exposure with a lppm ozone-air mixture, lasting 300 inspirations or approximately 10 minutes. After ventilation the dog was again put on $^{15}\text{N}_2$, (Fig. 3). Then a 5ppm ozone concentration in air was administered (Fig. 4) and a third nitrogen run (Fig. 5) completed this sequence.

Fig. 2, 3, 4 and 5 represent some typical results in the form of computer graphics, showing the distribution of annihilation activity for a particular plane between the detector heads of the camera, integrated over about 150 inspirations. The original 100 x 100 matrix is compressed into a 64 x 64 array for practical reasons. Left and right lungs are characterized by two peaks (Fig. 2) with a depression just forward of these indicating the location of the heart with only a low level of $^{15}\text{N}_2$ -activity. Just below the focal plane, appearing diffused, is the trachea. By choosing a different focal plane the trachea, having a diameter a little more than 1 cm, can be brought out somewhat more clearly.

Fig. 4 shows a 5ppm ozone exposure. The peak in the animal's trachea near the camera edge appears to indicate some preferred ozone absorption in the upper region of this airway. It should be pointed out however, that the specific activity of the ozone-air mixture is quite low to begin with, because the ratio of activated ozone to normal ozone achieved to date is only about 10^{-9} . In addition, the chemical separation of $^{15}\text{O}_2$ and $^{16}\text{O}_3$ after irradiation and prior to administration to the dog, takes perhaps 3 half-lives (6 minutes) before counting can actually begin; this results in relatively low counting statistics for the ozone exposures. On the other hand, the $^{15}\text{N}_2$, having a 10 minute half-life and requiring in general no chemistry, poses no such problems. Combining the results of pre- and post-ozone nitrogen runs, Fig. 2 shows a symmetric $^{15}\text{N}_2$ distribution. Following the lppm ozone treatment, the nitrogen activity observed in Fig. 3 indicates a reduced ventilation in the right lung wing which further decreased after the administration of the 5ppm ozone concentration (Fig. 5). Considerably more detail is obtained from the digital maps for which there is no room here, but the graphical data representation suffices to show that regional functional changes can be detected. More recent experiments have provided better quality of information, i.e. more detail, by improved experimental procedures and higher specific gas activities. In addition, promising results have been obtained from blood perfusion measurements using

$^{15}\text{O}_2$ and $^{16}\text{O}_3$ tracers.

It is clear that the most important single factor limiting quality of detail that can be obtained with a positron camera is the range of the positrons in matter of interest, i.e. animal or human tissue, bone, blood, etc. It has been pointed out above that the maximum range (3-4 cm) of the highest energy positron from ^{15}O in lung tissue is considerably larger than the intrinsic resolution (1.5 cm) of the camera. We are planning to investigate the quantitative effect of particle range on the camera resolution for biologically important isotopes.

Acknowledgments: The authors thank Don Freeman of Livermore for ably preparing the software that generates the graphic data displays, and C. D. Bowman, E. Goldberg and R. E. Yoder for suggesting this project and for many helpful discussions.

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[†]Work supported in part by the U.S. Atomic Energy Commission and the National Institute for Occupational Safety and Health, Public Health Service, Department of Health, Education and Welfare, OH 00340-06

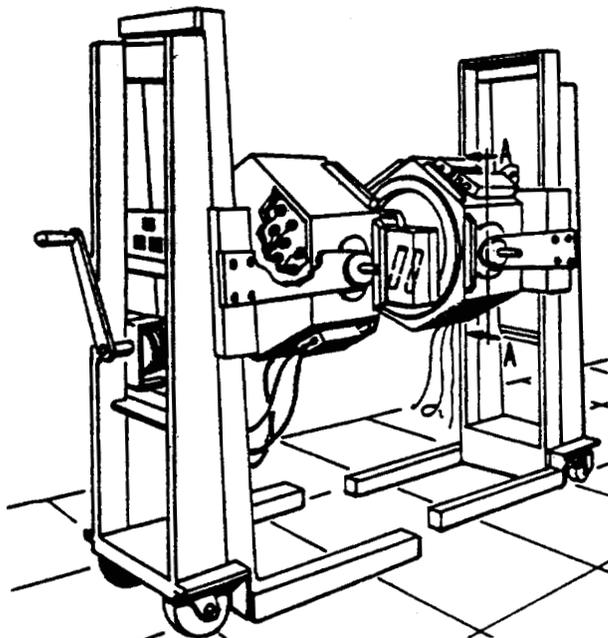


FIG. 1a, POSITRON CAMERA

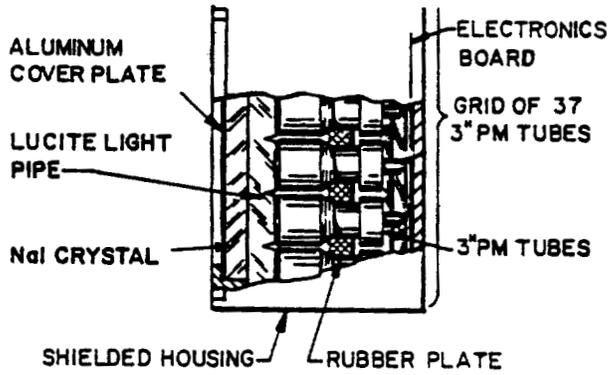


FIG. 1b, POSITRON CAMERA, DETAIL A-A

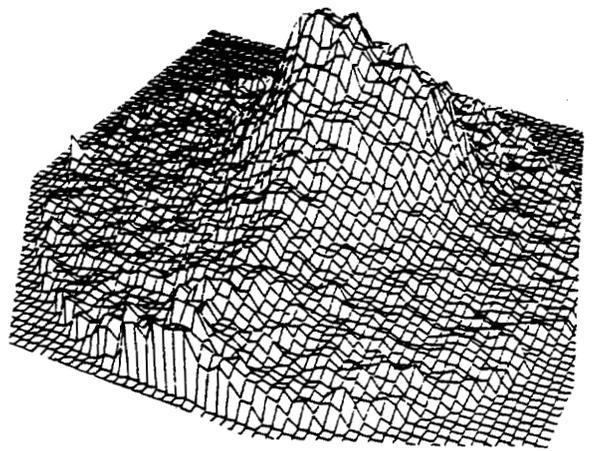


FIG. 3, NITROGEN UPTAKE
POST 1PPM OZONE EXPOSURE

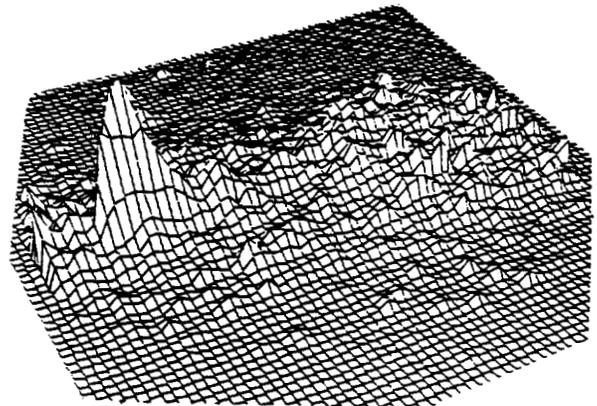


FIG. 4, 5PPM OZONE UPTAKE

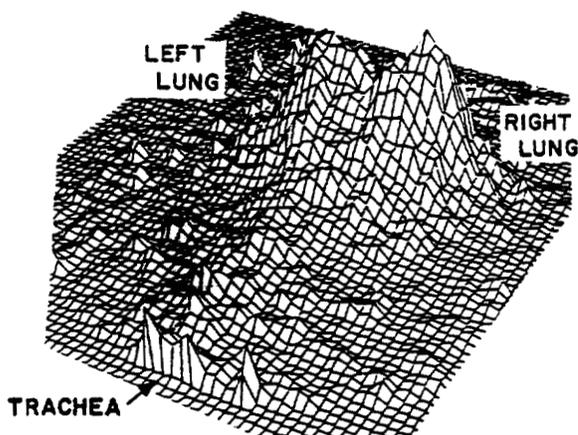


FIG. 2, NITROGEN UPTAKE
PRE-OZONE EXPOSURE

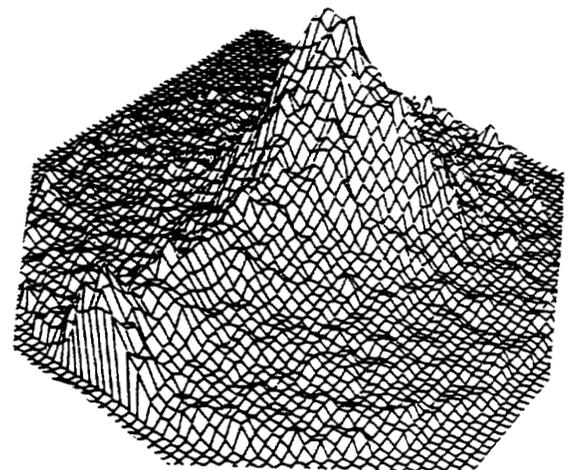


FIG. 5, NITROGEN UPTAKE
POST 5PPM OZONE EXPOSURE