717850

HUMAN SUBJECT EXPERIMENTS WITH AIR TAGGED WITH RADIOISOTOPES ^{13}N and ^{15}O

PREFACE

The Laboratory's basic safety policy is that operations must be planned and conducted in a manner that will prevent injury to personnel or damage to property. The minimum safety rules and practices necessary for achieving an accident-free work environment for the human subject experiments with air tagged with radioisotopes in Building 194 are stated in this Operational Safety Procedure.

Everyone in this building, i.e., visitor, maintenance and service employee, and regularly assigned employee, is required to abide by this procedure and the LLNL Health & Safety Manual to protect himself and other personnel from injury. Regular building personnel are responsible for assisting others in the building to understand the safety regulations relating to what they are doing and to abide by the safety requirements.

This procedure was prepared by building management assisted by Hazards Control. Confer with the Hazards Control safety team assigned to this building for interpretation of this procedure and for planning your operations to comply with safety requirements. Each individual in this building shall use this guidance effectively to avoid injury.

This Operational Safety Procedure has been reviewed by:

R. W. Bauer	E-Division
H. W. Patterson	Hazards Control
J. S. Johnson	Human Subject Committee

This Operational Safety Procedure is approved by:

John D. Anderson
Associate Director
for Physics

REPOSITORY LLNL B361, Rm. B940A
COLLECTION Institutional Review Board
BOX No. IRB Protocol File
FOLDER Meyer, P. IRM No. 80P-109
Decompression Sickness Studies
with Radioactive Gases
Folder 1 of 2

1121861

HUMAN SUBJECT EXPERIMENTS WITH OZONE AND AIR TAGGED WITH RADIOISOTOPES ^{13}N and ^{15}O

A. INTRODUCTION:

1. General

The purpose of this study is to measure the rate of nitrogen-uptake and elimination in the body of normal healthy humans.

The experiments will involve breathing of ^{13}N labelled air for about 30 minutes. Measurements may also require the subject to inspire a single breath of air, tagged with the radioisotope ^{15}O, and hold his/her breath for up to 30 seconds.

2. Changes

Any required change in operations that alters the scope or significantly decreases safety control will not be made until a revision or supplement to this procedure has been signed by the person authorized to approve this OSP. Any required change in operations that does not decrease the safety control may be made with the joint concurrence of the LINAC Operations Manager and the Hazards Control Safety Team Leader.

B. SCOPE

1. This procedure authorizes the exposure of human subjects to the following:

   a) Breathing of air tagged with ^{13}N for 30 minutes. This procedure can be repeated twice per subject.

   b) Breathing a single breath of air tagged with the radioisotope ^{15}O and holding his/her breath for up to 30 seconds. This procedure can be repeated a total of 3 times per subject.

C. HAZARDS ANALYSIS:

1. Radiation Hazards

Estimates of radiation dose from the ^{13}N and ^{15}O activities are based on calculation (see letter from G. Ozaki) and measures activities at maximum LINAC power. Activities at beam shut-off time are: ^{15}O: 0.3 mCi/liter; ^{13}N: 0.25 mCi/liter. Concentrations to be used in breathing mixtures will be:

a) $*N_2$ (80% or less) + O_2 (~20%) (non-radioactive)

b) $*O_2$ (20%) + N_2 (80%) (non-radioactive)

1121862

The shortest time possible from beam shut-off to administration of gas to subject is 4 minutes and the tidal volume for one deep breath is ~1.5 liters. The estimated activity then is, at t=4 minutes:

a) Act. (^{13}N) = (0.25) (0.80) (.76) = 0.152 mCi/liter

Act. (^{15}O) = (0.30) (0.20) (0.25) = 0.015 mCi/liter

The expected dose to the lung of the subject is then:

a) ^{13}N-dose/30 min exposure = (856) (.152) = 130 mrads

b) ^{15}O-dose/30 sec exposure = (16.6) (.015) = 0.25 mrads

Each subject may be given two nitrogen and three oxygen exposures bringing the maximum total dose to 260 mrads to the lung.

2. Gas Hazards (O_3, NO_2)

To generate the ^{13}N isotope, high-purity N_2 is irradiated with bremsstrahlung. Some trace of O_2 always is present and in this ionizing environment, NO_2 and N_2O forms. The concentration is controlled by minimizing the presence of O_2 in the nitrogen.

To produce ^{15}O, medical grade O_2 is used as a target gas. During irradiation, ozone (O_3) is formed in addition to NO_2 and N_2O. The latter two are again generated from trace amounts of N_2 present in the oxygen. The ozone is removed by passing the irradiated oxygen through an activated charcoal filter. The N_2 concentration in the oxygen is minimized to keep the NO_2 contaminant at a safe level.

3. The Operational Controls in paragraph F will reduce the above hazards to an acceptabe level.

D. RESPONSIBILITIES:

1. Supervisor

Paul Meyer is responsible for assuring that all work is performed in conformance with this OSP and the LLNL Health & Safety Manual. In his absence, the experiment will be terminated and a responsible person will be trained for the experiment.

2. Employee

All participating employees are responsible for performing their work according to the regulations of this OSP. They are expected to take all reasonable precautions to protect themselves and their fellow employees and to perform only those tasks that they believe can be accomplished safely. When participants have any doubt regarding the safety of any phase of their work, they are expected to check with the project supervisor before proceeding.

3. Hazards Control

The Hazards Control Safety Team assists management to institute and to maintain a low-risk work environment. In addition, Hazards Control may request that management or employees stop an operation when there appears to be an imminent danger to personnel or property (see Health & Safety Manual Section 1.06).

E. MATERIAL CONTROLS:

1. The target gases are:

a) O_2: Medical grade oxygen, U.S. Pharmacopia.

b) N_2: High purity nitrogen (silver colored bottles with pink top).

2. Waste gas disposal is achieved with large volum blower which pumps gas from the site of the experiment to the outside of Bldg. 194 at the roof level.

F. OPERATIONAL CONTROLS:

1. All human subjects shall receive a whole body radiation scan by Hazards Control before and after inhalation of radioactive gases.

2. The radioactive gases shall be filtered with a HEPA filter before inhalation by the subjects. A visual inspection of the filter cartridge gaskets and canister will be made prior to filter installation. Only an approved and tested filter cartridge obtained from Hazards Control Respirator Service will be installed in the filter canister.

3. Radioactive gas preparation:

The evacuated target gas bottle, located in the 0° cave, is filled from a standard gas cylinder containing either high-purity nitrogen (N_2) or medical oxygen, (O_2). Upon filling, the gas is being irradiated by LINAC bremsstrahlung.

In the case of N_2 as target gas, any undesired by-products come from small oxygen concentrations in the gas bottle. This can lead, in principle, to NO_2 and N_2O. Tests performed previously by Hazards Control personnel, found concentrations of less than 1 ppm of NO_2 and less than 22 ppm of N_2O in an irradiated sample.

In the case of O_2 as target gas, appreciable amounts of O_3 are formed. Less than 1 ppm of CO was found to be generated by the beam. The gas, after irradiation, is passed through activated charcoal to remove all ozone. The breathing mixture will be tested for NO_2 and ozone before it is administered.

G. PROCEDURE

a) Evacuate target-gas bottle in 0° cave to $\leq$50 microns.

b) Fill target bottle to ~600 psi with LINAC beam off.

c) Dump gas to reduce residual concentration from previous fill gas.

d) Refill bottle and irradiate.

e) Bleed radioactive gas as described below for nitrogen or oxygen.

Nitrogen $*N_2$

i) Mix active N_2 with clean O_2 to 4 parts $*N_2$ and 1 part O_2 in plastic bag.

ii) Check mixture for NO_2 ($\leq$5 ppm).

Oxygen $*O_2$

i) Let gas flow through charcoal trap to remove O_2. Mix with clean N_2 to give a ~20% O_2 concentration.

ii) Test for O_3 ($\leq$0.3 ppm).

Exposure Procedure

$*N_2$:

The prepared and tested gas mixture is taken from Trailer 930 to the subject in Bldg. 194 in a plastic bag which is then connected to the breathing valve. The subject then breathes for ~30 minutes from the bag. The exhaled gas is passed through a soda lime trap to remove all CO_2 before returning to the bag. A concentration of ~20% O_2 is maitained in the bag and monitored with a bio-marine oxygen deficiency meter or equivalent prior to use. At the end of the 30 minute period the bag is removed and the subject breathes room air with the washout being vented to the outside of Bldg. 194.

$*O_2$:

The prepared and tested gas is taken to Bldg. 194 in the manner described above. The subject takes one deep breath and holds it for 20-30 seconds, then exhales as described above.

4818Z/jp/172

1121865

APPLICATION TO NMRI COMMITTEE FOR THE PROTECTION OF HUMAN SUBJECTS

REF: SECNAVINST 3900.39A

I. PRINCIPAL INVESTIGATOR: Weathersby, P.K. LCDR, MSC, USN

II. ASSOCIATE INVESTIGATOR: Homer, L.D., Flynn, E.T., CDR, MC, USN
Meyer, P. (Livermore Laboratories)

III. TITLE OF RESEARCH PROJECT: Tracer Gas Kinetic Studies for Decompression Table Design.

IV. A. NO. The Livermore Committee will review the application before the experiments are begun.
B. N.A.

V. APPROXIMATE DATES OF RESEARCH: FROM: 8/80 TO: 9/81

VI. DESCRIPTION OF RESEARCH:

The project involves breathing a mixture of 20% oxygen and 80% Nitrogen 13 (up to 0.5 mci per liter) for a period of 30 minutes. The gas is equivalent to air except that the nitrogen is radioactive. For the 30 minutes of radioactive gas breathing and for the 60 minutes following, the subjects will be sitting in front of a radiation detection device (a positron gamma camera). The radioactive nitrogen is prepared on-site by bombardment of pure nitrogen with gamma rays.

Normal male volunteers from NMRI will be used. Six to ten subjects will be studied twice each. No medications will be used and no pain will be experienced. Only very minor discomfort will be felt from the requirement of breathing through a mouthpiece for 30 minutes and remaining immobile for 90 minutes.

Previous work by us at NMRI has established the feasibility of analyzing the type of data sought (1) and completed a similar study on anesthetized dogs (2). Mr. Meyer, our colleague at Lawrence Livermore Laboratory has several years experience in equipment operation (3), and animal and human experimentation using radioactive nitrogen (4).

VII. a. What are the risks that may or may not be encountered by subjects?

The only risks inherent in the procedure are those arising from the special gas breathed. Chemical risks arise from the possibility of creating noxious gases in the radioactive nitrogen preparation. These could include ozone and nitrogen dioxide. The major risk is radiological, that is, the unavoidable exposure of subjects to ionizing radiation. The total dose of radiation from the total of the two studies is estimated to not exceed 0.5 rad to the lungs and 0.01 rad to the body (5). This dose can be compared to the 0.18 rad/year of natural background exposure of the total population; 0.026 rad for a single chest x-ray; 5.0 rad/year, the current federal satutory limit for occupational exposure; and 4000 rads in clinical radiation therapy (6).

1121866

b. What are the safeguards against these risks:

The procedures to be used will attempt to minimize the chance of any chemical risks and to prevent any radiation exposure above the amount stated above. The radioactive nitrogen will be prepared using techniques developed by P. Meyer. Only very pure nitrogen will be exposed to the gamma-ray source (LINAC electron beam with water scatter). After activation, samples of the gas will be taken and immediately analyzed for ozone, nitrogen dioxide and N-13 activity. This analysis will be performed by the Livermore Hazards Control Department which is not otherwise involved with the research. Only when these analyses are completed will the nitrogen-oxygen mixture be breathed by the subject. Expired gases will be directly vented outside the lab building to prevent any other exposure. Subject doses will be calculated by standard methods (5) since the major exposure is too localized and transient to be directly measured.

c. What benefit will science or the subject potentially realize?

No direct benefits will be realized by the subjects. Indirect benefits may be realized by U.S. Navy divers, a group that is expected to provide the majority of subjects. The project is designed to provide data on the rate of nitrogen uptake and elimination in the human body. Decompression sickness among divers is thought to be caused by an inability to remove the excess nitrogen from a diver's body after breathing high pressure air. Prevention of decompression sickness is approached by adherence to decompression tables that are calculated to match the rate of nitrogen removal with the rate of diver return to normal pressure. The study proposed will attempt to provide the data necessary for NMRI to provide the safer decompression tables required by 1982.

The procedures are well established at the Livermore laboratory and are well accepted nationally in the field of experimental physiology. The equipment and expertise are too specialized for any accepted clinical standard.

VIII. Informed consent is attached.

REFERENCES

1. Weathersby, P.K., E.E.P. Barnard, L.D. Homer, and K.G. Mendenhall. Stochastic description of inert gas exchange. J. Appl. Physiol: Respir. Exercise Environ. Physiol. 47:1263-69.

2. Weathersby, P.D., K.G. Mendenhall, E.E.P. Barnard, L.D. Homer, S. Survanshi, and F. Vieras. The distribution of xenon gas exchange rates in dogs. J. Appl. Physiol.: Respir. Environ. Exercise Physiol., in review, 1980.

3. P. Meyer, E. Behrin, R. Frank, R. Holub, and C.E. McJilton. Biomedical application of shortlived positron emitting isotopes. In: Schrack, R.A., Bowman, C.D., (Eds). Nuclear cross sections and technology. Washington, D.C.: National Bureau of Standards Special Publication 425 469-471, 1975.

1121867

4. Meyer, P., M. Morgan, R. Holub, and R. Frank. Comparison of overall and regional lung mechanical function in dogs upon ozone exposure. The Physiologist 22:87, 1979.

5. Lawrence Livermore Laboratory Memo. (Written by M.S. Singh, and T.R. Crites, Hazards Control Department, to P. Meyer, Accelerator Division). Dec. 13, 1976.

6. The effects on population of exposure to low levels of ionizing radiation. National Academy Science, National Research Council, Washington, D.C., Nov. 1972.

1121868

CONSENT TO PARTICIPATE VOLUNTARILY

PROJECT TITLE: Tracer Gas Kinetic Studies for Decompression Table Design.

PRINCIPLE INVESTIGATOR: Weathersby, P.K. LCDR, MSC, USN

ASSOCIATE INVESTIGATOR: Homer, L.D., Flynn, E.T.,CDR, MC USN, Meyer, P.

I do hereby give my consent to serve as a test subject in a joint Naval Medical Research Institute - Lawrence Livermore Laboratory study. The study will involve my twice breathing a mixture of oxygen and radioactive nitrogen while sitting in front of a radiation detection device. I understand that the study is designed to measure how fast nitrogen enters and leaves parts of the human body. This information is needed to develop safer diver decompression schedules. I also understand that this study will provide no direct benefit to me.

I have been informed that this study is voluntary and that I may withdraw from it at any time. My questions have been answered and I know that the investigators will answer any other questions I may have.

I have been informed that the only discomfort that I should expect will follow from 30 minutes of breathing through a mouthpiece and from 90 minutes of sitting very still. I understand that there is a small risk of breathing a chemically harmful gas such as ozone or nitrogen dioxide. I also understand that I will receive a radiation dose from the study. I have been informed that this does is within the ranges used in medical procedures and less than the dose currently allowed by law for people who work with radioactive materials. I have been told that there is still a very small risk of disease such as cancer from this amount of radiation.

DATE_____ SIGNED_____

_____
(TYPED, NAME, RANK, RATE OR GRADE)

DATE_____ WITNESSED_____
(NOT DIRECTLY INVOLVED IN PROJECT)

_____
(TYPED NAME, RANK, RATE OR GRADE)

1121869

RECOMMENDATION OF COM TEE FOR THE PROTECTION OF H AN SUBJECTS

PRINCIPAL INVESTIGATOR: P.K. WEATHERSBY, LCDR MSC USN

TITLE OF RESEARCH PROJECT: Tracer gas kinetic studies for decompression table design.

In our opinion the protocol and safeguards described on the attached application are adequate to meet the standards of U.S. Navy in regard to experiments utilizing people; namely that the rights and welfare of individuals will be respected, that the individuals or those responsible for their care have given their informed consent, and that potential benefits outweigh any risk involved. Review and approval by the Committee for the Protection of Human Subjects is hereby requested.

INVESTIGATOR: P.K. WEATHERSBY, LCDR MSC USN DATE: 6 May 80

PROGRAM CENTER HEAD: MARK E. BRADLEY CAPT MC USN DATE: 5-7-80

THE COMMITTEE FOR THE PROTECTION OF HUMAN SUBJECTS RECOMMENDS:

APPROVAL X DISAPPROVAL ____

OF THE ABOVE NAMED PROTOCOL AS A RESULT OF A REVIEW ON 27 May 80 (DATE)

COMMENTS:

PERIODIC REVIEW SUGGESTED: ANNUALLY X SEMI ANNUALLY ____ QUARTERLY ____

J. R. FLETCHER, CAPT MC USN
Chairman, Human Use Committee

REVIEWED APPROVAL BY HUMAN USE COMMITTEE MEMBERS

CAPT. R. M. ELDER, CHC, USN, NNMC

CDR T. PALMER, MSC, USN, NMRI

T D. L. HAGENGRUBER, JAG, USNR, NNMC

T J. MATTHEWS, MC, USNR, NMRI

RS. T. SAYLER, SUPERVISORY LIBRARIAN

RS. P. GOLDBERG, COMMUNITY REPRESENATIVE

4121870