

Mail Station L- 54

Ext: 7861

July 8, 1977

TO: Paul Meyer (L-28)

FROM: David C. Shepherd

SUBJECT: Human Subjects Approval: Ozone Effect on Lung Function

This memorandum will confirm that at the May 31, 1977, meeting the Lawrence Livermore Laboratory Human Subjects Committee approved the use of human subjects in a collaborative program with the University of Washington entitled "Ozone Effects on Overall and Regional Lung Function."

This approval is based upon the approval of the University of Washington Human Subjects Review Committee and is subject to the following additional conditions:

1. There must be a California-licensed physician present while the experiments involving humans are taking place;
2. The Laboratory will require a statement from the University of Washington holding the Laboratory harmless from any liability arising out of these experiments;
3. We will require a certificate of insurance from the University of Washington indicating current insurance coverage for the risks associated with these experiments;
4. The radiation exposure should be held to the lowest levels possible;
5. The experimental procedures are to conform to those described in the application to the University of Washington Human Subjects Committee, except that the subjects will not exercise on a treadmill. Any changes to the protocol must be approved in advance by the LLL Committee;
6. The experimenters must notify the Committee immediately if any complications for human subjects develop during the course of the experiments; and
7. The experimenters must use the consent form approved by the University of Washington Human Subjects Committee.

This approval will become effective upon receipt by the Laboratory of the hold harmless agreement and the certificate of insurance from the University of Washington, and will remain valid until May 30, 1978. We will contact the University of Washington in the near future to work out the administrative arrangements.

*D. C. Shepherd*  
 D. C. Shepherd  
 Secretary, LLL Human Subjects  
 Committee

 University of California  
**LAWRENCE LIVERMORE LABORATORY**

Distribution: Human Subjects Committee Members

BOX NO. FRB Minutes  
 FOLDER Human Subject Minutes and Approvals 1975-1977

REPOSITORY LLL B361 Rm B940A  
 COLLECTION INSTITUTIONAL Review Board

APPLICANT: REPEAT GRANT NUMBER SHOWN ON PAGE 1 →		GRANT NUMBER	
SECTION IV—SUMMARY PROGRESS REPORT		5 RO1 HL 18925-3	
PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (Last, First, Initial)		PERIOD COVERED BY THIS REPORT	
Frank, Robert		FROM	THROUGH
NAME OF ORGANIZATION		7/1/76	6/30/77
University of Washington			
TITLE (Repeat title shown in Item 1 on first page)			
Ozone Effects on Overall and Regional Lung Function			

1. List publications: (a) published and not previously reported; (b) in press. Provide five reprints if not previously submitted.
2. List all additions and deletions in professional personnel and any changes in effort.
3. Progress Report. (See Instructions)

1) Objectives:

- a) To determine the sequence and possible interrelations of early functional changes caused by low concentrations of ozone in dogs and humans.

Goals for 7/1/76 - 6/30/77:

- b) 1) Complete the study on the effects of 0.45 ppm of ozone on both regional and overall functional performance in 3 to 4 additional dogs.
  - 2) Obtain more data at 0.23 ppm of ozone; only three healthy dogs had been studied at this level.
  - 3) Improve the computer programs to handle the regional function data.
  - 4) Obtain permission from University of Washington and Lawrence Livermore Laboratory to study human subjects using the same experimental protocol (regional and functional measurements before and during ozone exposure).
- 2) a) Work completed: Twenty experiments were carried out at Lawrence Livermore Laboratories since the last progress report of May, 1976. Of these twenty dogs, three were exposed to 0.45 ppm O<sub>3</sub>, four were exposed to 0.23 ppm O<sub>3</sub>, four were exposed to 0.13 ppm O<sub>3</sub> and nine were control dogs with no ozone exposure.

Permission was obtained from the University of Washington Human Subjects Review Committee and Radiation Safety Committee for the use of human subjects using the same experimental protocol (regional and functional measurements before and during ozone exposure).

Preliminary Results:

Activated N<sub>2</sub> Distribution:

Methods of analyzing these data are currently being explored. One approach considers the steady-state distribution of inspired gas before and after exposure to ozone or to ozone-free air. A rectangular grid equally divided into 25 to 30 sectors is superimposed on the lung and the steady-state count rate in each sector is normalized by the count rate for the entire lung. This estimates the fraction of inspired gas delivered to each region over many breaths. The ratio of this fraction in the baseline period to that after exposure is a measure of the change in regional distribution.

2004028

Figures 1-4 show the ratio of baseline fraction ( $C_{\text{regional}}/C_{\text{lung control}}$ ) to exposure fraction ( $C_{\text{regional}}/C_{\text{lung exp}}$ ) sectors of lung (animal supine, plane view parallel to the spine). A ratio of 1.0 indicates no change on exposure. The solid curves show ratios after the two hour baseline period, and the dashed curves show ratios after three hours of ozone exposure. A quantitative measure of the change in distribution of gas is the ratio's root-mean-square difference from 1.0, which is calculated for each row of sectors and indicated in the figures as  $\Delta_{\text{rms}}$ . This parameter was also calculated for the entire lung (summing over all sectors) and is tabulated below. (Table 1).

Compared to the sham-exposed (control) dog, two of three dogs exposed to 0.23 ppm ozone showed increased maldistribution of inspired gas. Greater changes were typically seen in the peripheral regions, both laterally and head-to-tail.

**TABLE 1** Change in regional steady state  $N_2$  distribution, compared to the control state.

Dog	Ozone, ppm	Elapsed Time, Hrs.	$\Delta_{\text{rms}}$ (overall)
59	0	2 hr. baseline	.079
		3 hr. exposure	.078
55	0.23	2 hr. baseline	.279
		3 hr. exposure	.251
56	0.23	1 hr. exposure	.252
		3 hr. exposure	.369
57	0.23	2 hr. baseline	.112
		3 hr. exposure	.320

#### Standard Respiratory Function Measurements

Analysis of the standard functional data for the same dogs for which we have radioactive data (55,56,57, and 59) show borderline changes in central airway caliber (a slight decrease in maximal flow volume peak flow) in dog 56 and peripheral airway narrowing (a decrease in dynamic compliance) in dog 55. No significant changes were seen in dogs 57 and 59.

#### b) Technical Problems

Analysis of the enormous quantities of data collected during the radioactive measurements is finally progressing at a satisfactory rate. In the past problems have been encountered in writing a program to analyze the data (originally collected on a PDP-15 computer) on the Livermore CDC-7600 computer. The present computer program allows for area integration of radioactivity distribution in different positron camera focal planes and also provides very versatile capabilities for graphic display.

#### i) Significance

Our hypothesis is that low concentrations of  $O_3$  may alter functions that are related to the patency of the peripheral airways in the absence of significant increases in resistance of the central airways (i.e., in the presence of only minor increases in  $R_L$ ). To what extent regional ventilation/perfusion relations are altered by  $O_3$  is not known. The hypothesis, if substantiated, may signal a direction for functional tests that are used in epidemiological studies.

#### i) Research goals for the coming year

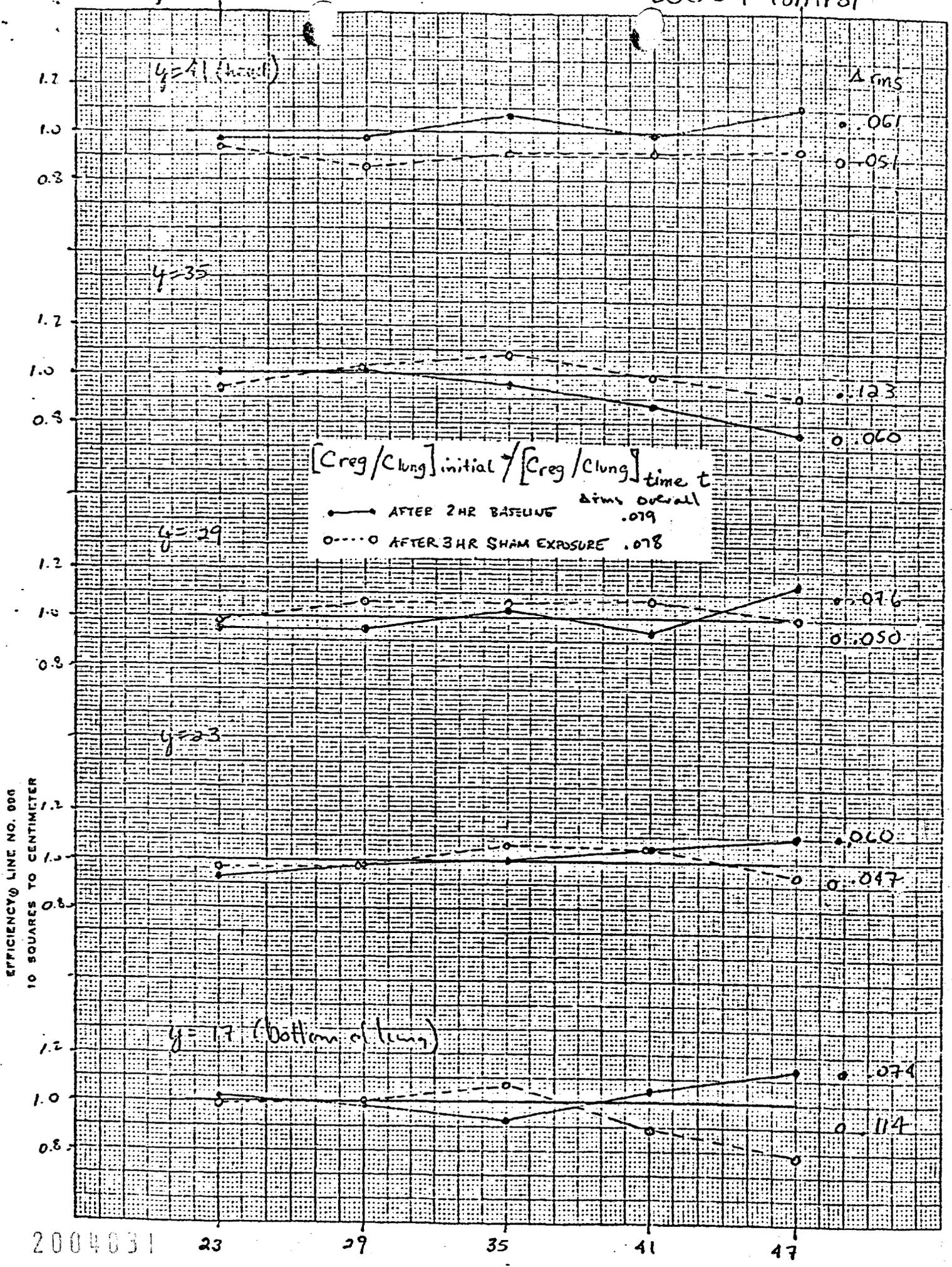
a) Continue to improve radioactive data analysis methods.

- b). Complete data analysis of the remainder of dog data.
- c) Obtain data on eight human subjects, sixteen experiments total (control and exposure), at 0.2 ppm  $O_3$  for a two-hour exposure.

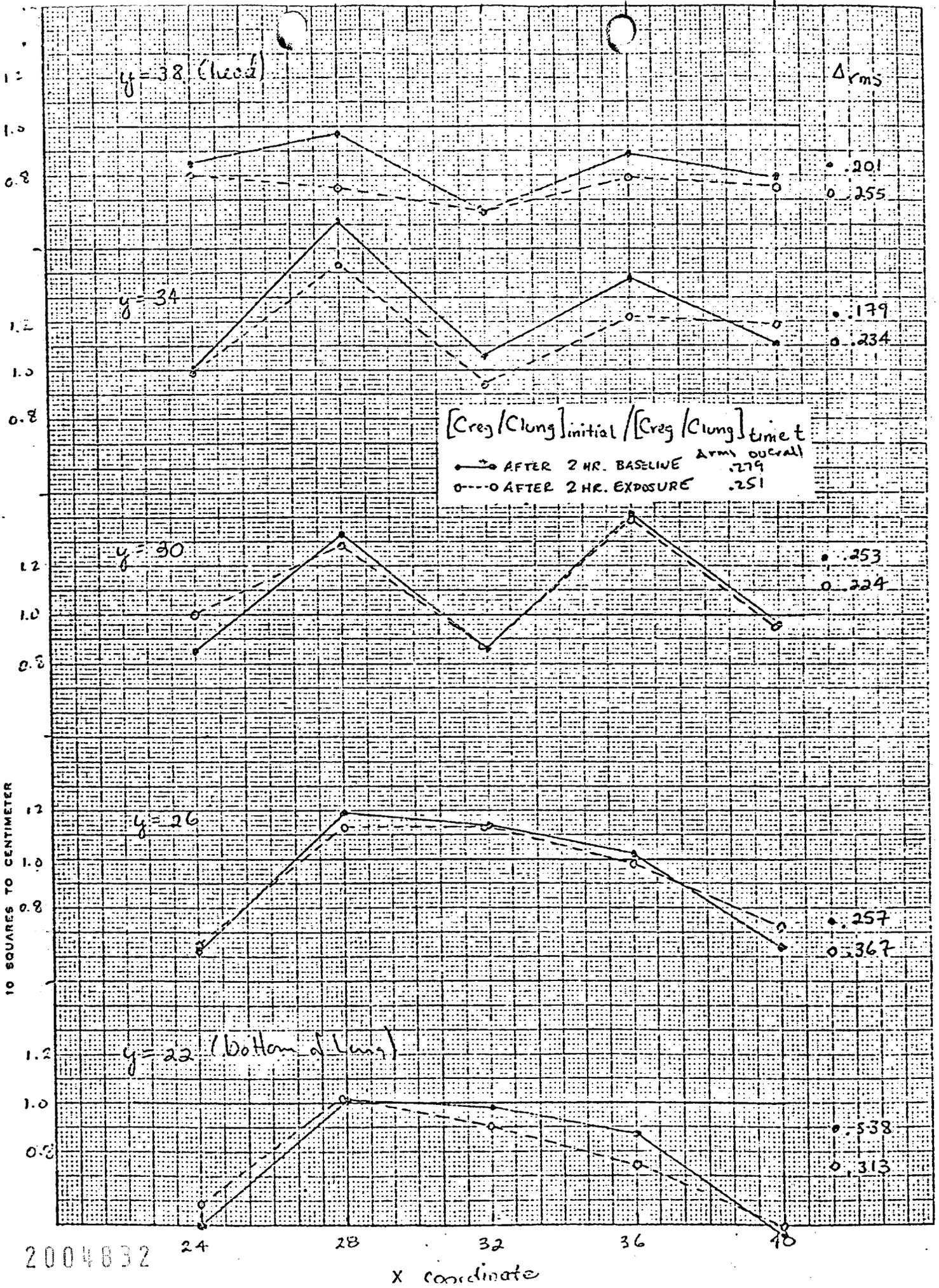
The undersigned agrees to accept responsibility for the scientific and technical conduct of the project and for provision of required progress reports if a grant is awarded as the result of this application.

25 April, 1977  
Date

Robert Frawley  
Principal Investigator or  
Program Director

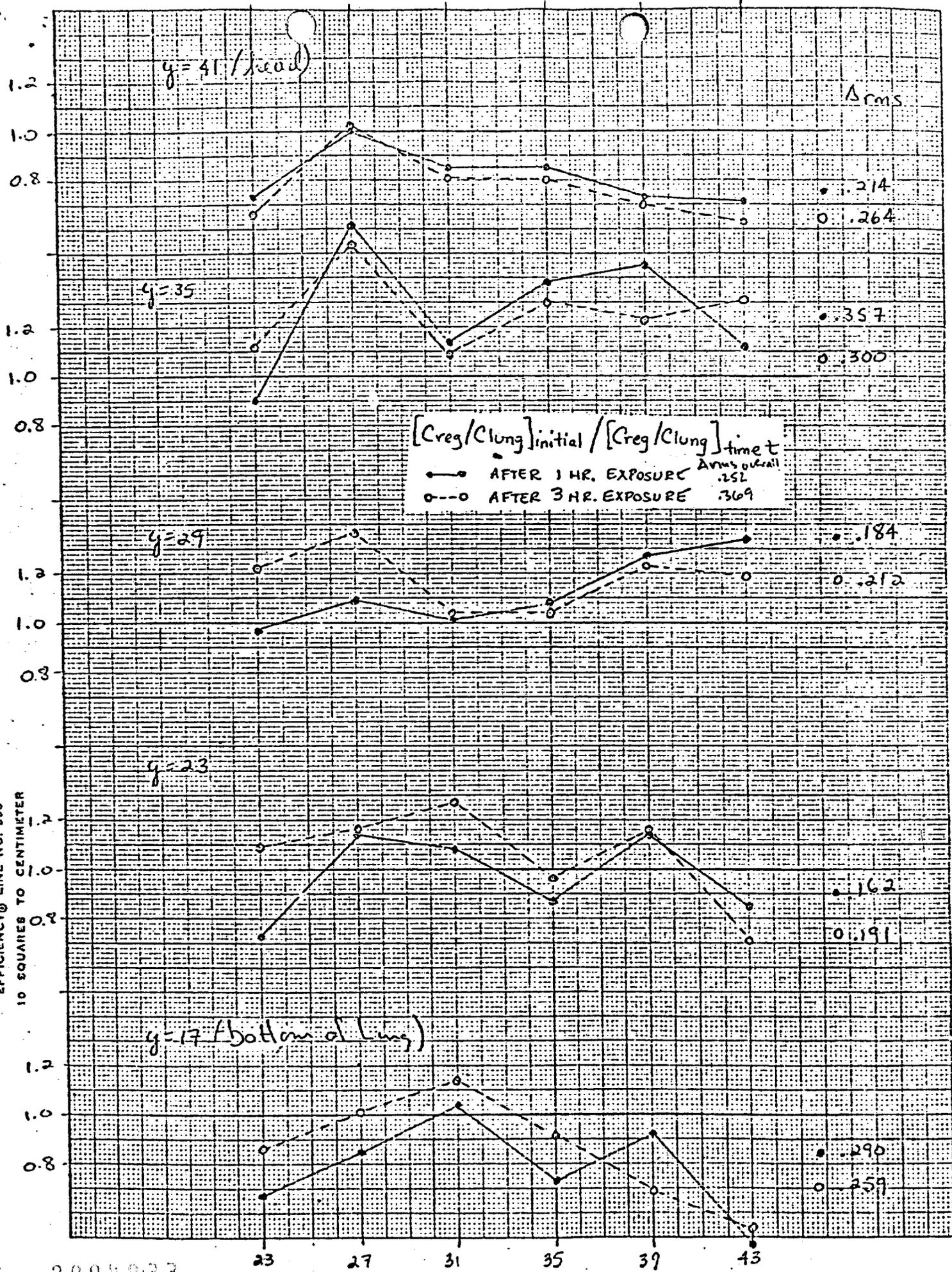


EFFICIENCY @ LINE NO. 095  
10 SQUARES TO CENTIMETER

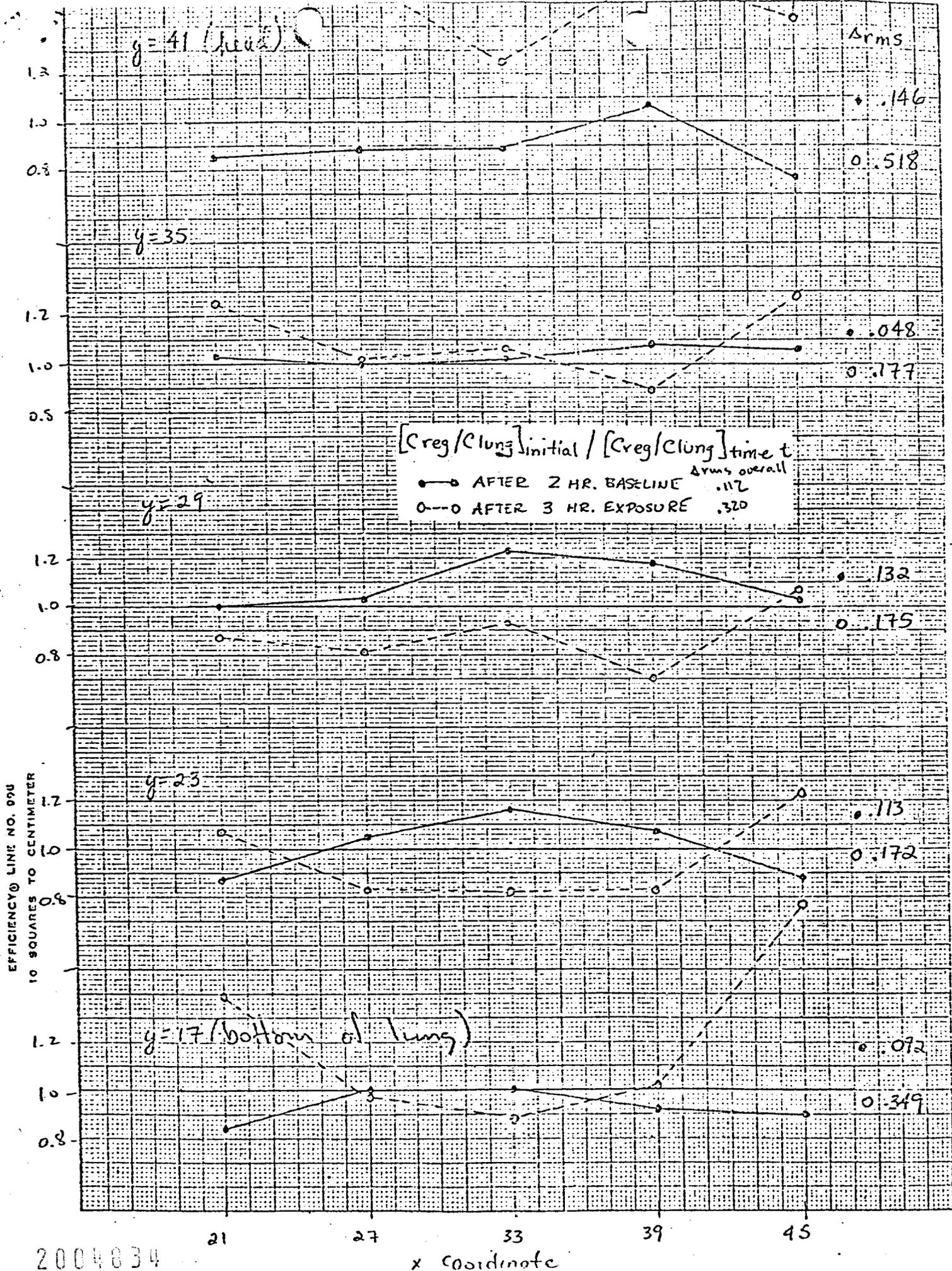


2004832

EFFICIENCY LINE NO. 986  
10 SQUARES TO CENTIMETER



2004833



ADMINISTRATIVE ESCORT REQUEST

(PLEASE TYPE)

18129

NO.

DATE REQUIRED: 10/13/77 TIME: FROM: 1:45 TO: 4:05

VISITOR(S) NAME AND AFFILIATION: David B. Gordon Veterans Hospital

BUILDING(S) AND ROOM(S) TO BE VISITED: B-123 Conference Room A

MEET AT: SOUTH BADGE OFFICE  WEST BADGE OFFICE

PRIMARY ADMINISTRATIVE ESCORT: Vivian James DEPT. DO EXT. 7861 BLDG. 111 RM. 415

ADMINISTRATIVE ESCORTS: David C. Shepherd

PURPOSE OF VISIT: Attendance at LLL Human Subjects Committee

IF CAR PASS IS REQUIRED PLEASE EXPLAIN:

LIST BUILDING COORDINATOR THE PRIMARY A.E. HAS CONTACTED FOR EACH BUILDING THE VISITOR WILL ENTER:

David C. Shepherd	21	<i>[Signature]</i>	DO	7861
AUTHORIZED REQUESTER	MAIL CODE	SIGNATURE	DEPARTMENT	EXT.

MAIL REQUEST TO BADGE OFFICE, BLDG. 310, RM. 120-L-370. THIS REQUEST MUST BE IN THE HANDS OF ISSUE OFFICE PRIOR TO VISIT. IF NECESSARY, PLEASE HAND CARRY TO ASSURE PROMPT SERVICE.

*[Signature]* 10/12/77

2004835