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EFFECTS OF VARIOUS DOSE RATES OF MIXED
NEUTRON-GAMMA RADIATIONS ON THE
LD50(60) RESPONSE OF SHEEP

T. S. Mobley, et al

Air Force Weapons Laboratory

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) This report covers the final portion of large mammal radiobiology research conducted by the Air Force Weapons Laboratory's Biophysics Division. This work was completed in June 1970. One hundred sixteen adult female sheep were exposed at three different dose rates of mixed neutron-gamma radiations from a Godiva-type reactor. Experimental animals received right unilateral irradiation, midline air exposures (MAE), ranging from 165 to 472 rads at a high (5:1) neutron-to-gamma (over)		

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ratio. Dose rates of 10^1 , 10^5 , and 10^8 rads per minute were employed in these studies. Radiation exposures were monitored by thermoluminescent gamma detectors, fission foils, and activation foils. Sixty-day median-lethal-dose ($LD_{50(60)}$) values were: 377 rads at a dose rate of 10^1 rads/min, 373 rads at a dose rate of 10^5 rads/min, and 369 rads at a dose rate of 10^8 rads/min. The $LD_{50(60)}$ values were not significantly different. Death frequency distribution and mean survival times were compared on animal groups irradiated with similar doses but differing dose rates of mixed neutron-gamma radiations. No dose-rate effects were noted over the range of exposures tested. Sixty-day lethality values for sheep irradiated at the differing dose rates were combined and treated as a single experiment. Probit analysis of these data yielded an $LD_{50(60)}$ value of 370 rads, MAE, with 95 percent confidence limits of 351 to 387 rads. The corresponding $LD_{50(60)}$ value and 95 percent confidence limits expressed in terms of midline tissue dose were 166 rads (158 to 174).

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PREFACE

The information contained in this report was presented at the 19th Annual Meeting of the Radiation Research Society, Boston, Massachusetts, May 9-13, 1971.

The experiments were conducted according to the standards in the Guide for Laboratory Animal Facilities and Care, 1965, prepared by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences - National Research Council; the regulations and standards prepared by the Department of Agriculture; and Public Law 89-544, Laboratory Animal Welfare Act, August 24, 1966.

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SECTION I

INTRODUCTION

This report summarizes certain biological responses in sheep unilaterally exposed at three different dose rates of reactor-produced neutron-gamma radiations. The radiations employed in the studies were from a fission weapon simulator, the Sandia Pulsed Reactor (SPR), yielding a 5:1 neutron-to-gamma ratio.

Previous reports from the Air Force Weapons Laboratory (AFWL) have shown no significant difference in 60-day median-lethal-dose ($LD_{50(60)}$) values for bilaterally irradiated sheep (refs. 1, 2, and 3) exposed at dose rates of 3×10^4 or 2×10^8 rads per minute or between bilaterally and right unilaterally irradiated sheep exposed at a dose rate of 2×10^8 rads per minute (ref. 3). The radiation source employed in previous studies was the SPR I, a pulsed reactor of limited output requiring two pulses to obtain doses in the mid-lethal range, i.e., 250 to 600 rads midline air exposure. A criticism of the previous studies was that exposures were separated in time by approximately 75 minutes. The irradiations thus delivered were fractionated doses and did not qualify as near-instantaneous exposures in the sensu stricto. In 1967 the SPR I critical assembly was replaced by a super Godiva-type reactor (SPR II). The new critical assembly had a greatly increased output. Exposures up to 1000 rads per pulse at distances adequate to ensure uniformity of dose to a number of large mammals positioned in an arc around the critical assembly became possible.

The objectives of this experiment were: (1) to determine the radiation response in sheep irradiated at dose rates of 10^1 , 10^5 , and 4×10^8 rads per minute, (2) to compare the radiation response following a single right unilateral exposure with previously determined response (ref. 3) to two right unilateral exposures separated by 75 minutes, and (3) to quantitatively report any differences in dose-rate effects in a large mammal exposed to a fission-weapon-like spectrum of radiations.

SECTION II

MATERIALS AND METHODS

RADIATION SOURCE

The source of simulated fission weapon radiations used in this study was the Sandia Pulsed Reactor (SPR II). The design and operating characteristics of the reactor are described in references 4 and 5. The characteristics pertinent to this study are briefly summarized as follows: (1) SPR II uses 93-percent-enriched uranium, 10-weight-percent molybdenum fuel assembly; (2) the 105-kg unreflected enriched uranium assembly is a right circular cylinder approximately 8 inches in diameter by 8-1/2 inches high; (3) the reactor has a capability of running steady-state power up to 1.5 kW, has a programmed burst mode of approximately 50-microseconds duration, full-peak width at half-maximum height, and has a delayed scram operation so that a very small burst spike is followed by a tail whose duration was extended out to 200 milliseconds for these studies. Approximately 90 percent of the dose was delivered during the elongated 200-millisecond, tail portion of the burst. The reactor was lowered into a below-floor-level storage vault following irradiation.

EXPOSURE CONDITIONS

Animal exposures were accomplished a distance of 175 cm from the center of the assembly. Usually eight animals were simultaneously exposed. On one exposure day, two groups of only six sheep each were irradiated. The animals were exposed in aluminum cages positioned on aluminum tables. Movement of sheep within the cages was restricted by the use of a canvas body sling that prevented the subject from lying down in the cage.

While in the exposure room, subjects were observed over closed circuit television. The irradiated sheep were retrieved approximately 30 minutes post-exposure and were returned to indoor holding pens where they were maintained under standardized husbandry procedures (ref. 6).

Radiation doses were calculated from: (a) thermoluminescent gamma detectors, (b) fission foils, and (c) activation foils according to routine procedures in use at this laboratory (ref. 7). Each exposure was monitored by two complete

dosimetry packages. The reported dose values represent the averaged response of all dosimeters.

EXPERIMENTAL SUBJECTS

One and one-half to 3-year-old adult female sheep of the Columbia-Rambouillet cross were used in these studies. The subjects were purchased from a local supplier and maintained under the standardized conditions of this laboratory (ref. 6). Irradiations were accomplished between 0800 and 1400 hours.

SECTION III

RESULTS

SUMMARY OF EXPOSURE PARAMETERS

The various aspects of the exposure conditions are summarized in table I. Steady-state irradiations were accomplished at a reactor power level of 500 watts. In one instance, the power level was 166 watts. Exposure times at 500 watts ranged from 23 to 34 minutes at a dose rate of 14 rads per minute. In the single case in which sheep were irradiated for 34 minutes at a power level of 166 watts, the dose rate was 4.85 rads per minute. The measured neutron dose and gamma dose for each irradiation are reported. The neutron-to-gamma ratio ranged from 6.1:1 to 5.0:1 for the six exposures and averaged 5.6:1.

Millisecond (average dose-rate 10^5 rads/min) and microsecond exposures (average dose rate 4×10^8 rads/min) are reported in table I. The temperature rise, Δt , of the fuel assembly during pulsed operation, rad dose caused by neutrons, rad dose caused by gammas, total dose, and neutron-to-gamma ratio are reported for the three 200-millisecond and the six 50-microsecond exposures. Neutron-to-gamma ratios ranged from 5.1:1 to 6.1:1 and averaged 5.5:1 for microsecond exposures and 5.3:1 for millisecond exposures.

60-DAY MORTALITY RESPONSE

The 60-day mortality responses of sheep exposed to dose rates of 10^1 (steady state), 10^5 (200 millisecond), and 4×10^8 (50 microsecond) rads per minute are summarized in table II. Midline air exposures ranged from 165 rads to 472 rads. Thirteen groups of eight animals each and two groups of six animals each received mixed neutron-gamma radiations. Animals exposed to doses of 165 rads steady-state and 278 rads 200-millisecond pulse did not experience any mortality. Exposures of 430 rads (microsecond) and 472 rads (steady-state) killed all subjects. Exposures of 310 rads and above resulted in death to some of the irradiated subjects. Fifty-seven of 116 irradiated sheep died. Twenty-seven control sheep were sham-irradiated and observed throughout the course of the experiments.

DEATH FREQUENCY DISTRIBUTION

Table III and figure 1 summarize the dates of death following irradiation for the different dose rates and doses. The mean survival time for decedents at each

Table I

DOSE SUMMARY: STEADY-STATE AND PULSED IRRADIATION

Exposure (min)	Power Level (watts)	Rads		Total	Neutron/Gamma Ratio
		Neutron	Gamma		
34	166	140	25	165	5.6:1
23	500	279	56	335	5.0:1
26	500	310	53	363	5.8:1
30	500	349	57	406	6.1:1
32	500	394	70	464	5.6:1
34	500	402	70	472	5.7:1

Average neutron-to-gamma ratio = 5.6:1

EXPOSURE TIME--50 MICROSECONDS

Change in Core Temperature Δt	Rads		Total	Neutron/Gamma Ratio
	Neutron	Gamma		
80	260	50	310	5.2:1
86	278	51	329	5.4:1
86	291	56	347	5.2:1
90	320	53	373	6.0:1
100	358	59	417	6.1:1
108	362	68	430	5.3:1

Average neutron-to-gamma ratio = 5.5:1

EXPOSURE TIME--200 MILLISECONDS

Change in Core Temperature Δt	Rads		Total	Neutron/Gamma Ratio
	Neutron	Gamma		
69	235	43	278	5.5:1
92	311	59	370	5.3:1
110	368	72	440	5.1:1

Average neutron-to-gamma ratio = 5.3:1

Table II

DOSE RESPONSE DATA ON SHEEP EXPOSED TO FISSION SPECTRUM RADIATION

Dose Rads	Exposure Mode	Number Dead/ Number Exposed	60-Day Mortality Percent
276	Millisecond	0/8	0.0
370	Millisecond	4/8	50.0
440	Millisecond	7/8	87.5
310	Microsecond	3/8	37.5
329	Microsecond	3/8	37.5
347	Microsecond	2/8	25.0
373	Microsecond	2/8	25.0
417	Microsecond	5/8	62.5
430	Microsecond	8/8	100.0
165	Steady State	0/8	0.0
335	Steady State	1/6	16.7
363	Steady State	4/8	50.0
406	Steady State	5/8	62.5
464	Steady State	5/6	83.3
472	Steady State	8/8	100.0

Table III

DEATH FREQUENCY DISTRIBUTION OF SHEEP EXPOSED TO FISSION SPECTRUM
(NEUTRON-GAMMA) RADIATION

Exposure Mode	Dose Rads	Days on Which Deaths Occurred	Mean Survival Time (Days*)
	165	---	>60
Steady-State	335	6	6.0
Dose Rate			
10 rads/min	363	4,4,6,13	6.7
	406	4,5,6,14,28	11.4
	464	5,5,7,7,49	14.6
	472	5,5,5,5,6,6,31,33	12.0
	278	---	>60.0
Millisecond	370	4,5,5,34	12.0
Dose Rate			
10^5 rads/min	440	5,5,6,6,8,10,37	11.0
Microsecond	310	4,4,4	4.0
Dose Rate			
4.8×10^8 rads/min	329	5,8,13	8.7
	347	6,9	7.5
	373	4,11	7.5
	417	4,7,9,10,11	8.2
	430	4,4,5,5,5,5,10,35	9.1

*Mean survival time calculated only for those animals dying during the 60-day observation period.

Mean survival time all decedents 9.98 days

Median survival time all decedents 5.50 days

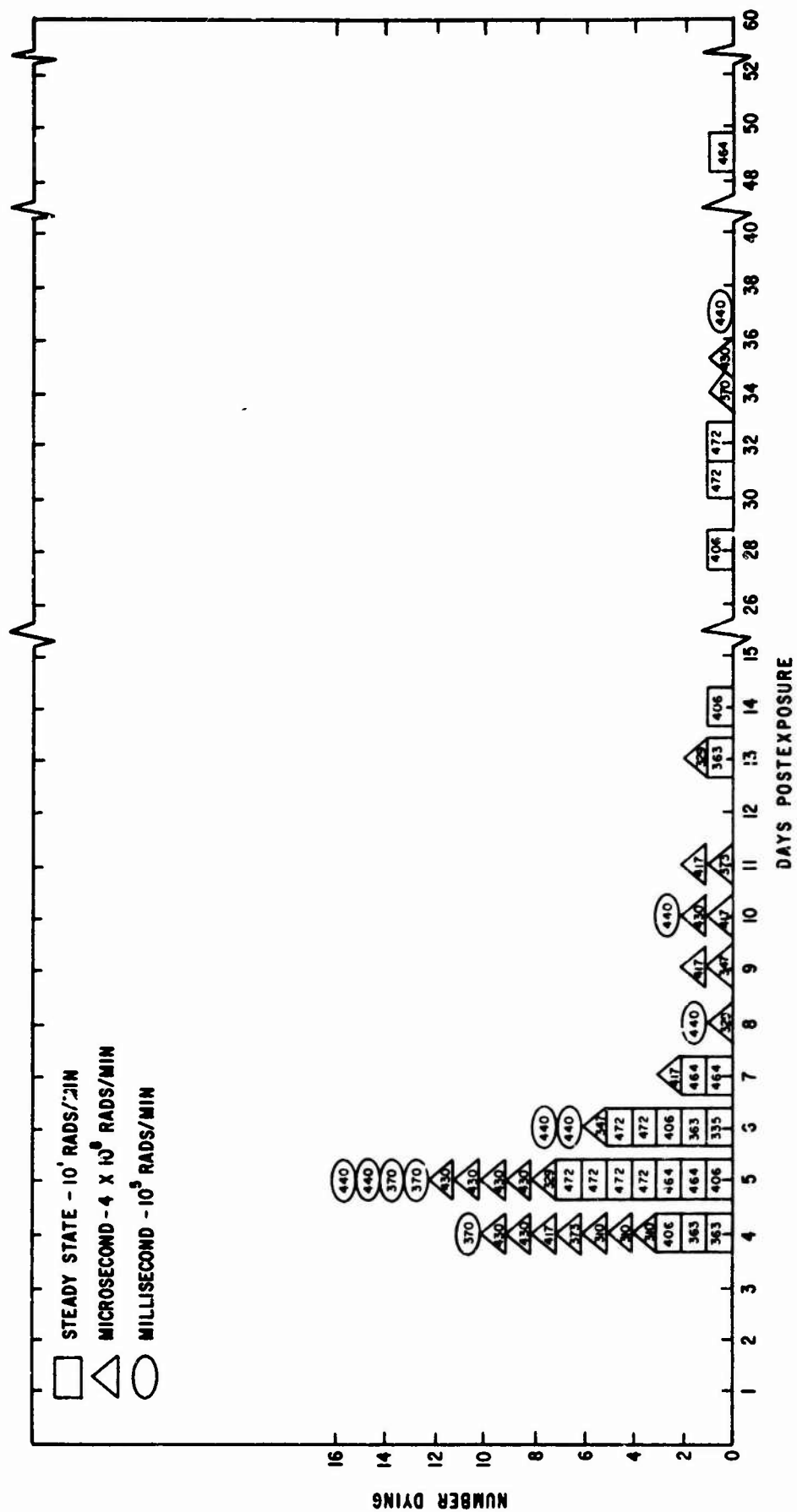


Figure 1. Death Frequency Distribution for Neutron-Gamma Irradiated Sheep.

dose rate and dose level is reported. The earliest deaths occurred 4 days following irradiation, and the last death occurred on the 49th post-irradiation day. The mean survival time for all decedents was 10 days.

The data from table III are displayed in graphic form in figure 1. This presentation suggests a bimodal death frequency distribution. Fifty of 57 decedents (88 percent) died between the 4th and 14th post-exposure days. Seven of 57 decedents (12 percent) died between the 28th and 49th post-exposure days. Exposure doses ranging from 310 rads to 363 rads produced deaths in the 4th to 14th day post-exposure category. Exposure doses ranging from 368 rads to 472 rads produced some deaths between the 4th and 14th post-irradiation days; and in six of eight exposure groups, deaths during the 28th to 49th post-irradiation days.

PROBIT ANALYSES OF DATA

Probit analyses (ref. 8) of the 60-day mortality data are summarized in table IV and figure 2. The regression lines for the steady-state, millisecond, and microsecond exposures were plotted by using the computer solution of the 10, 50, and 90 percent lethal doses (figure 2A). Experimental points (open circles for the steady-state, open triangles for the millisecond, and crosses for the microsecond exposures) are plotted. The computed $LD_{50(60)}$ values were 377 rads for steady-state, 373 rads for millisecond, and 369 rads for microsecond exposures. The 60-day median-lethal-dose values were not significantly different. The data from all the dose rate studies were combined and subjected to probit analysis. The computed regression line and slope for the combined data treatment are presented in figure 2B. The $LD_{50(60)}$ value for sheep exposed to right unilateral neutron-gamma radiation at dose rates ranging from 10^1 to 4×10^3 rads per minute was found to be 370 rads. The 95-percent confidence limits were 351 to 387 rads. The slope of the regression line was 13.13 ± 2.42 .

EFFECT OF PRE-EXPOSURE BODY WEIGHTS

Table V lists the pre-exposure body weight in pounds for each subject exposed to the indicated dose and dose rate of neutron-gamma radiation. Body weights of nonsurviving sheep are underlined. The number in parentheses following each underlined weight is the survival time, in days, for the decedent. The average pre-exposure body weight for sheep that survived the irradiation was 95.6 pounds (range 75 to 122 pounds). The average pre-exposure body weight of all sheep that died following irradiation was 94.3 pounds (range 74 to 133 pounds). Comparing

Table IV

COMPUTED 60-DAY MEDIAN-LETHAL-DOSE ($LD_{50(60)}$) VALUES AND SLOPES FOR SHEEP
EXPOSED TO THE INDICATED DOSE RATES OF MIXED NEUTRON-GAMMA RADIATION

Exposure Mode	Dose-Rate (Rads/Min)	$LD_{50(60)}$ (Rads)	95-Percent Confidence Limits	Slope	Standard Error
Steady State	10^1	377	333 to 406	6.62	± 2.05
Millisecond	10^5	373	318 to 415	7.70	± 2.85
Microsecond	4×10^8	369	310 to 485	10.16	± 4.41
Combined	---	370	351 to 387	13.13	± 2.42

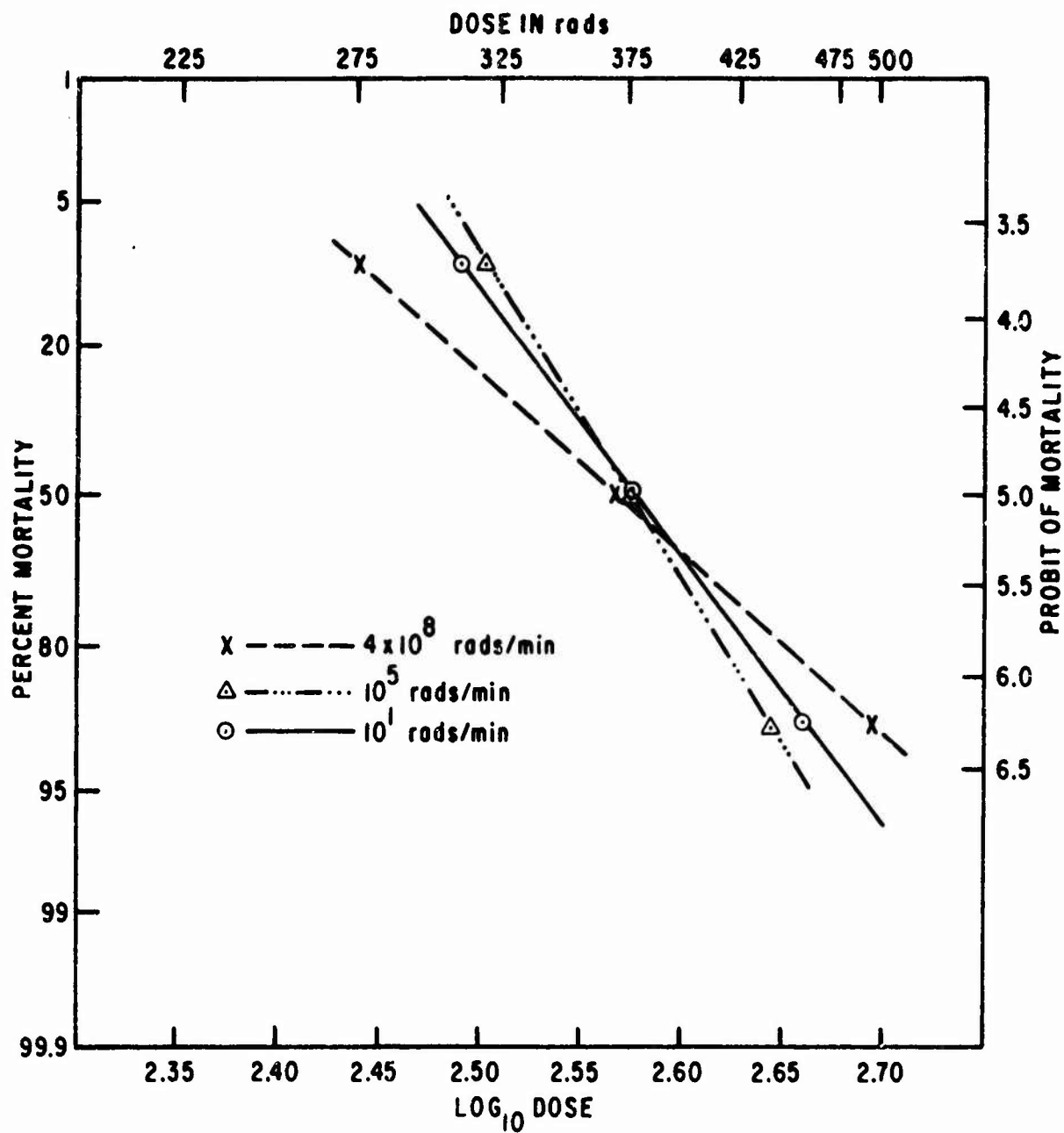


Figure 2a. Comparative Regression Line (Probit) Analysis for Neutron-Gamma Irradiated Sheep Exposed at Different Dose Rates.

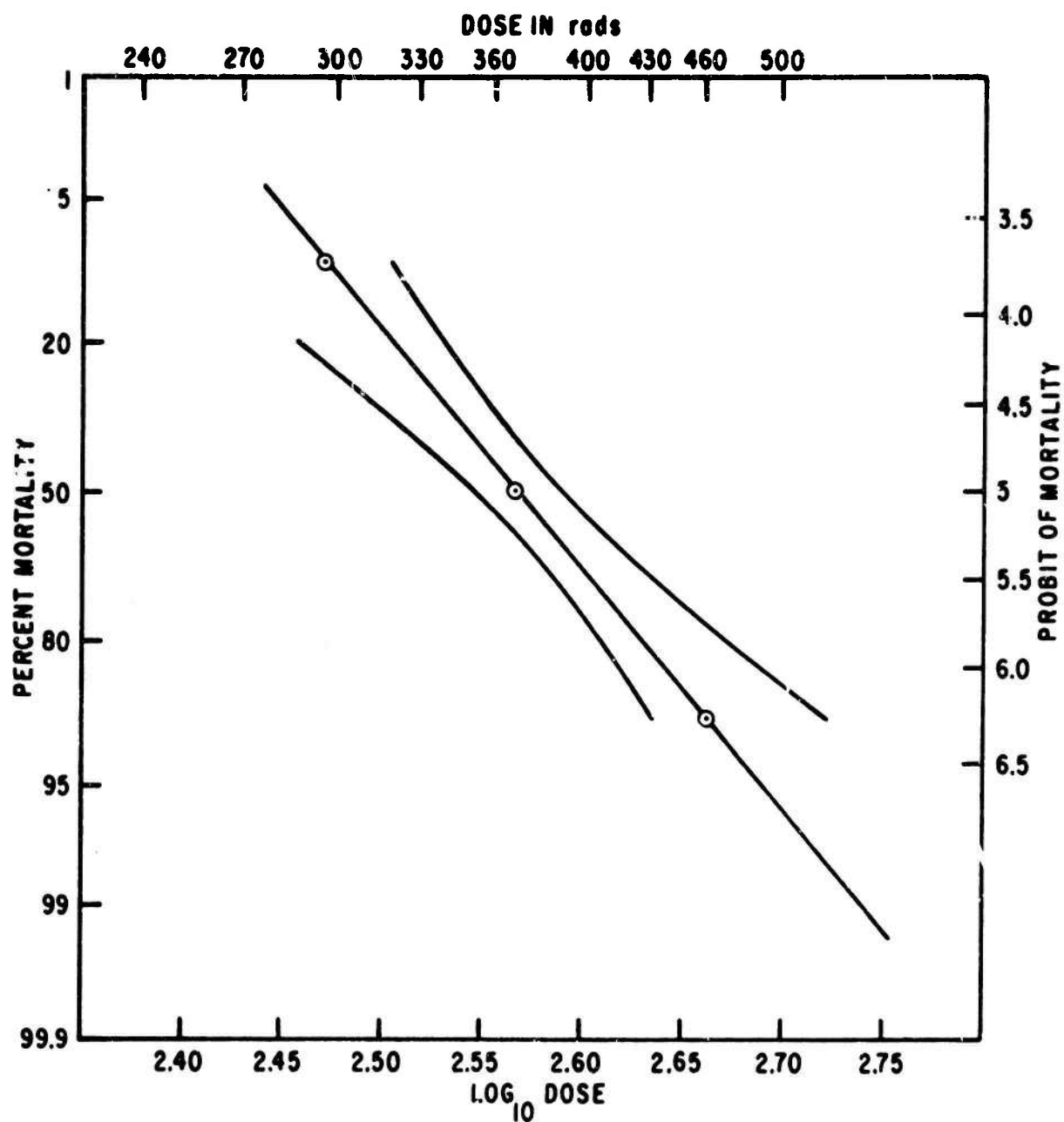


Figure 2b. Combined Regression Line (Probit) Analysis for Neutron-Gamma Irradiated Sheep.

Table V

PREIRRADIATION BODY WEIGHTS AND SURVIVAL TIMES OF SHEEP EXPOSED AT THREE
DIFFERENT DOSE RATES

Dose Rate (Rads/Mir.)	Dose Rads	Preirradiation Body Weight in Pounds
10 ⁵	278	100, 97, 120, 92, 85, 75, 94, 100
	370	87, 112, 115, <u>80</u> (34), <u>80</u> (5), <u>95</u> (4), 84, <u>94</u> (5)
	440	<u>100</u> (37), 87 (6), <u>100</u> (6), <u>112</u> (8), <u>95</u> (5), <u>100</u> (10), <u>92</u> (5), 95 $\bar{m}$ Survivors 97 $\bar{m}$ Nonsurvivors 94
4 x 10 ⁸	310	<u>115</u> (4), <u>100</u> (4), 98, 115, 105, 97, 111, <u>112</u> (4)
	329	90, 95, <u>83</u> (13), 95, <u>77</u> (8), <u>88</u> (5), 77, 90
	347	105, <u>113</u> (6), <u>100</u> (9), 100, 95, 115, 122, ?
	373	89, 87, <u>78</u> (11), 82, 82, <u>91</u> (4), 87, 82
	417	75, <u>74</u> (4), <u>87</u> (9), 94, <u>78</u> (11), <u>77</u> (7), <u>75</u> (10), 93
	430	<u>112</u> (5), <u>110</u> (5), <u>100</u> (5), <u>92</u> (10), <u>100</u> (35), <u>102</u> (4), <u>110</u> (5), <u>108</u> (4) $\bar{m}$ Survivors 96 $\bar{m}$ Nonsurvivors 94
10 ¹	165	122, 108, 112, 108, 111, 107, 108, ?
	335	79, 83, 87, 79, <u>75</u> (6), ?
	363	89, <u>76</u> (4), <u>93</u> (6), 84, 94, <u>82</u> (13), <u>90</u> (4), 83
	406	<u>84</u> (4), <u>88</u> (5), <u>93</u> (6), <u>100</u> (14), <u>95</u> (28), 78, 100, 95
	464	80, <u>80</u> (5), <u>84</u> (5), <u>83</u> (7), <u>80</u> (7), <u>82</u> (49)
	472	<u>109</u> , (6), <u>97</u> (6), <u>112</u> (31), <u>110</u> (5), <u>118</u> (5), <u>107</u> (5), <u>133</u> (5), <u>106</u> (33) $\bar{m}$ Survivors 94.5 $\bar{m}$ Nonsurvivors 94.65

? Weight not recorded

Average weight all survivors 95.62

Average weight all nonsurvivors 94.26

all surviving sheep against all nonsurviving sheep, the differences in preexposure body weight were not statistically significant.

SECTION IV

DISCUSSION

This study did not reveal significant dose-rate effects (within the range tested) on $LD_{50(60)}$ values for sheep subjected to mixed neutron-gamma radiations. The findings of this investigation are in agreement with the results of Ainsworth *et al.* (ref. 9). That group reported no significant differences between $LD_{50(60)}$ values for mice exposed to reactor-produced radiations at a rate of 40 rads/min or 10^6 rads/min. Similarly, the $LD_{50(60)}$ for Macaca mulatta was reported to be unaffected by differing dose rates of TRIGA radiations delivered at a rate of 20 rads/min (ref. 10) and 10^6 rads/min (ref. 11).

In table VI are summarized the $LD_{50(60)}$ values, 95-percent confidence limits, mean survival times, and standard deviations for the previously reported findings (refs. 1, 2, and 3) and this study. The findings were obtained at a high, 5:1, neutron-to-gamma ratio; and are for subjects exposed bilaterally or right unilaterally to two doses separated in time by 75 minutes. The findings of the current study were obtained on subjects receiving a single right unilateral exposure.

If one compares the $LD_{50(60)}$ values and 95-percent confidence limits of sheep receiving either two right unilateral exposures or a single unilateral exposure, it is apparent that no significant differences occurred. Likewise, if one compares the $LD_{50(60)}$ values and 95-percent confidence limits on sheep unilaterally irradiated, right side, with two pulses of mixed neutron-gamma radiations with sheep exposed to a single right unilateral pulsed exposure of either milliseconds or microseconds duration, it is apparent that there were no significant differences.

The results of the study reported in this communication indicate there are no dose-rate effects at median-lethal-dose values for sheep exposed to pulsed neutron-gamma radiation delivered in time periods of milliseconds, microseconds, or at a dose rate of 14 rads/min.

The results of combining the groups irradiated with a single exposure delivered at the various dose rates (table IV and figure 2) produced an $LD_{50(60)}$ value of 370 rads with 95-percent confidence limits of 351 to 387 rads midline

Table VI
COMPARATIVE LD₅₀₍₆₀₎ VALUES AND MEAN SURVIVAL TIMES OF SHEEP EXPOSED TO BILATERAL OR RIGHT
UNILATERAL NEUTRON-GAMMA RADIATIONS

Exposure Aspect	Number Exposures	Dose Rate (Rads/Min)	LD ₅₀₍₆₀₎	95 Percent Confidence Limits	Number	Mean Survival Time (Range)	Reference AFWL Technical Report No.
1. Bilateral	2	10 ⁴	402	391-413	33	14.39(4-29)±6.712	68-94
2. Bilateral	2	10 ⁸	404	390-419	21	16.43(9-35)±5.582	68-94
3. Bilateral	2	10 ⁸	360	335-420	32	13.38(4-49)±9.469	65-199
4. Unilateral	2	10 ⁸	367	329-398	27	11.18(4-41)±9.299	65-199
5. Unilateral	1	4 x 10 ⁸	369	310-485	23	7.91(4-35)±6.550	This study
6. Unilateral	1	10 ⁵	373	318-415	23	11.36(4-37)±12.069	This study
7. Unilateral	1	10 ¹	377	333-406	23	11.26(4-49)±12.031	This study

Z values demonstrated that differences of combined mean survival times between bilaterally irradiated sheep, 1 through 3 above, and combined right unilaterally irradiated sheep, 4 through 7 above, were significant at the 0.01 level.

Students "t" test revealed that the differences between mean survival times of unilaterally irradiated sheep were not significant at the 0.2 level.

air dose (MAD). In a previous study (ref. 12) the relationship of midline air dose to midline tissue dose was determined. 46 percent of the MAD was found present at the midsagittal plane of a 100-pound, 28-cm diameter sheep cadaver. The cadaver used in the study was of the same approximate weight and diameter as the subjects used in the present study. Accordingly it is felt that a reasonable estimate for the $LD_{50(60)}$ values, expressed in terms of midline tissue dose, is obtained by multiplying the $LD_{50(60)}$ by 0.46. This value corresponds to a midline tissue dose of 170 rads with 95-percent confidence limits of 161 to 178 rads.

A majority of deaths, 70 percent, occurred between the 4th and 8th post irradiation days. Deaths during this time period are associated with severe gastrointestinal involvement. This finding is in marked contrast with the findings on sheep irradiated with 60-cobalt gamma rays (refs. 13 and 14). Median-lethal-dose levels of 60-cobalt cause deaths no earlier than the 17th postirradiation day.

SECTION V

SUMMARY

Sixty-day median-lethal-dose values were determined on sheep right unilaterally exposed to mixed neutron-gamma radiations delivered at dose rates of 10^1 , 10^5 , and 4×10^8 rads per minute.

$LD_{50(60)}$ values did not differ significantly with dose rates employed.

Data from the three dose-rate studies were combined and treated as a single experiment. Probit analysis yielded an $LD_{50(60)}$ value of 370 rads with 95-percent confidence limits of 351 to 387 rads, midline air exposure.

The $LD_{50(60)}$ value for sheep irradiated with a single pulse of mixed neutron-gamma radiations did not differ significantly from the $LD_{50(60)}$ values on sheep receiving two pulses separated in time by 75 minutes.

Mean survival times of decedents irradiated at dose rates of 10^1 , 10^5 , or 4×10^8 rads/min were not significantly ($P > 0.2$) different.

Mean survival times of bilaterally irradiated sheep were significantly ($P < 0.01$) longer than right unilaterally irradiated sheep.

Mixed neutron-gamma irradiation produces a preponderance of early, 4 to 8 days postirradiation, deaths. This finding is in contrast to the reported studies on 60-cobalt irradiated sheep in which deaths, at median-lethal-dose levels, do not occur until the third postirradiation week.

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