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Dose-Rate Effects for Mammary Tumor Development in Female Sprague–Dawley Rats Exposed to X and γ Radiation

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Mammary tumor development was followed in two experiments involving a total of 2229 female Sprague–Dawley rats exposed to various doses of X or γ rays at different dose rates. The data for another 462 rats exposed to tritiated water in one of these experiments were also analyzed. The incidence of adenocarcinomas and fibroadenomas at a given time after exposure increased linearly in proportion to total radiation dose for most groups. However, no significant increase in adenocarcinomas was observed with chronic γ exposures up to 1.1 Gy, and the increase in fibroadenomas observed with chronic γ exposures at a dose rate of 0.0076 Gy h^{-1} up to an accumulated dose of 3.3 Gy was small compared to that observed after acute exposures. The incidence of all mammary tumors increased almost linearly with the log of dose rate in the range 0.0076 to 26.3 Gy h^{-1} for 3 Gy total dose of γ rays. The effects of X rays appeared to be less influenced by dose rate than were the effects of γ rays.

INTRODUCTION

A previous publication from this laboratory was concerned with the relative biological effectiveness (RBE) of tritium β rays compared to chronic X rays for acceleration of the appearance of mammary tumors in female Sprague–Dawley rats (*1*). In that study, tritium β rays appeared to be about 1.1–1.3 times more effective in total tumor induction than chronic 200 kVp X rays. A comparison of chronic and acute X rays in the same study indicated that acute X rays were also slightly more effective than chronic X rays (*1*).

This first experiment also included a single group of animals exposed to 0.93 Gy ^{60}Co γ rays at a low dose rate and a group exposed to 0.60 Gy ^{60}Co γ rays at an

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TABLE I

Number of Animals in Each Group, Irradiation Type, Total Dose, and Dose Rate Used in the Two Experiments

Set	*Group*	*Number of animals*	*Radiation*	*Dose (Gy)*	*Average dose rate (Gy h^{-1})*
		Experiment 1			
CONT1[a]		199	—	0	0
HTO	HTO05[b]	110	Tritium	0.46	0.00192
	HTO10	113	Tritium	0.92	0.0038
	HTO19	120	Tritium	1.8	0.0074
	HTO44	119	Tritium	3.8	0.016
CX	CX029	120	X rays	0.29	0.0012
	CX057	120	X rays	0.57	0.0024
	CX110	120	X rays	1.10	0.0046
	CX200	120	X rays	2.00	0.0083
AX1	AX057	120	X rays	0.57	0.57
	AX178	112	X rays	1.8	1.78
AG	AG064	119	^{60}Co	0.64	0.60
CG	CG093	119	^{60}Co	0.93	0.002
		Experiment 2			
CONT2		120	—	0	0
AX2	AX050	60	X rays	0.62	37.2
	AX100	60	X rays	1.2	37.2
	AX200	60	X rays	2.5	37.2
	AX300	60	X rays	3.7	37.2
AG	AG050	60	^{60}Co	0.50	26.3
	AG100	60	^{60}Co	1.0	26.3
	AG200	60	^{60}Co	2.0	26.3
	AG300	60	^{60}Co	3.0	26.3
CG	CG050	60	^{60}Co	0.59	0.0076
	CG100	60	^{60}Co	1.1	0.0076
	CG200	60	^{60}Co	2.3	0.0076
	CG300	60	^{60}Co	3.4	0.0076
IG	IG001	60	^{60}Co	3.0	2.04
	IG002	60	^{60}Co	3.0	0.167

[a] Abbreviations: CONT, controls; HTO, tritiated water; CX, chronic X rays, AX, acute X rays; AG, acute γ rays; CG, chronic γ rays; IG, intermediate γ rays.

[b] Letters denote sets as in footnote a. Numbers are group numbers.

intermediate dose rate (see Table I). The excess number of mammary tumors appearing in both γ-irradiated groups was smaller than expected from the X-ray results, and particularly for the low-dose-rate group. The data were not reported at that time because results from a single group of animals were considered unreliable. Previous data from other laboratories suggested a possible decrease in mammary tumor re-

sponse when exposures to low-LET radiation were fractionated or protracted (*2–5*). Unfortunately, the data on which the analysis of the dose-rate effectiveness factor for chronic γ radiation was based (*6*) were rather sparse and the range of dose rates was relatively small (*3*). A second experiment was therefore carried out in our laboratory to examine in more detail the effects of dose rate on the acceleration of mammary tumor development in female Sprague–Dawley rats using various doses of ^{60}Co γ rays. In addition, the tumors from both experiments have been typed histologically and the data from both experiments have been analyzed in terms of the effects of radiation type, dose, and dose rates on types of mammary tumors observed. This paper reports the results of these analyses.

MATERIAL AND METHODS

Animals. As in the previous study (*1*). Sprague–Dawley female rats (specific pathogen free) were obtained from Charles River Canada, Inc., St. Constant, Quebec. The animals were 50–55 days old and weighed about 180 g (range 160–200 g) at the start of each irradiation. These animals were received in two separate shipments in December 1982 and January 1983. Sixty animals from each shipment were selected at random and served as controls.

Groups of 60 animals each were assigned to various radiation treatments as described below. The animals were fed Purina rat chow and water *ad libitum* and were kept at a room temperature of 24 ± 2°C. All studies were carried out in accordance with guidelines established by the Canadian Council on Animal Care.

Irradiation procedures. Four groups of rats were exposed to 200 kVp X rays at 37.2 Gy h^{-1} as shown in Table I. These are referred to as acute X-ray groups. The animals were placed in a circular, horizontal acrylic wheel (37 cm in diameter) with an acrylic top 0.3 cm thick. The wheel was placed centrally within the beam of a Muller MG 300 X-ray set (operated at 200 kVp and 17.5 mA) at a distance of 50 cm between the floor of the wheel and the X-ray tube surface plate.

For dosimetric determinations, an ion chamber was placed in one of the 14 compartments underneath an anesthetized rat. Additional animals were also placed in the two adjacent compartments. Readings were taken at various positions in the 360° radius and compared to readings of an ion chamber fixed at a reference point close to the wheel. During the experimental irradiations, a constant exposure rate was maintained by adjusting the beam current to maintain a constant reading of the reference ion chamber. The ion chamber measurements in roentgens were converted to grays using a factor 0.0095 for 200 kVp X rays (*7*).

Another four groups of rats were exposed to ^{60}Co γ rays at a high dose rate (26.3 Gy h^{-1}) as shown in Table I. These are referred to as acute γ-ray groups. The animals were restrained in acrylic tubes 8 cm inside diameter, 19 cm long. Animals were irradiated laterally with an unattenuated ^{60}Co γ beam, alternate animals being irradiated from the right and left sides, respectively, at a distance between the source and the center of each tube of 50 cm. Preliminary measurement of dose rate was achieved through an ion chamber placed in each of the tubes of the animal holders. Tissue dose in grays per roentgen was calculated using a conversion factor of 0.00966 (*7*). The standard deviation of doses received in the various restraining tubes was less than 8%.

Four additional groups of rats were exposed to ^{60}Co γ rays at low dose rate (0.0076 Gy h^{-1}) as shown in Table I. These are referred to as chronic γ-ray groups. The animals were placed, four to a stainless steel wire mesh cage (18 × 36 × 18 cm), in each of 16 cages in a stainless steel rack 4 m from the ^{60}Co source. A 0.5-cm lead shield was placed behind and beneath the rack to minimize scatter. To achieve the above dose rate at 4 m, the γ beam was attenuatec by inserting a 6.45-cm lead plug (with 0.2 cm brass on exit side) in the port of the ^{60}Co source. The dose rate was measured with an ion chamber placed at the center of each cage. Tissue dose in grays per roentgen was calculated using a conversion factor of 0.00966 (*7*) with a further attenuation factor of 0.727 to allow for shielding by 5 cm of soft tissue. The assumed value of 5 cm was adopted to take into consideration the shielding effect to the mammary glands of each of the four animals in each cage by its own body as well as by the other three companion animals, allowing for random animal movement. The standard deviation of doses received in the various cages was about 4%.

Two additional groups of animals were exposed to ^{60}Co γ rays at intermediate dose rates and are referred to as intermediate γ dose-rate groups. Exposures were carried out in a manner similar to those noted above for the chronic γ-ray groups but with decreased thicknesses of lead for attenuation and/or shorter distances between the γ source and the animals. The standard deviation of doses in various animal cages was 4 to 5%.

Irradiation procedures for the animals of Experiment 1 (Table I) are described in the previous report (*1*). This experiment included four groups of rats treated with tritiated water (HTO); in this case, average dose rates were calculated over the first 10 days after the first injection of HTO (Table I).

Scoring of mammary tumors. As in the previous study (*1*), all animals in each group were allowed to live until the cumulative number of animals with at least one mammary tumor exceeded 50% of the number at risk. The occasional animal was euthanized before this time because of impending death or discomfort caused by an inoperable tumor. Autopsies were performed on all animals and tissues appearing grossly abnormal were collected for histologic evaluation.

The animals were examined for mammary tumors periodically (every 1–3 weeks) by palpation. Individual records were kept for each rat, noting the anatomical location of each breast tumor and the time of its appearance since the day of the single acute exposure, the middle day of a chronic exposure period, or the 53rd day of age in the case of the control animals. Tumors were excised under anesthesia when they reached a size of 2.5 cm in diameter, and tissue sections were prepared for classification of the tumors. The animal was then returned to the experiment for observation of additional tumors. A tumor was to be an additional tumor if it met either of the following criteria: (a) It occurred at a location which had not previously produced a tumor. (b) It occurred at the site of a previous tumor, but was a different type of tumor.

The criteria for histological classification of mammary tumors were similar to those used previously by other investigators (*9–11*). This histological classification was extended to mammary tumor samples collected during the course of the previous study (*1*) as well as those collected during the present experiment. For the purposes of this analysis, the tumors have been classified in three categories: adenocarcinomas, fibroadenomas, and other. The "other" category accounts for only a small fraction of tumors, and consists of fibromas, fibrosarcomas, and lipomas, as well as occasional tumors that regressed spontaneously and were not typed. Typically adenocarcinomas and fibroadenomas account for greater than 90% of the total number of tumors in any group.

The tumor incidence was corrected for mortality by a life table method (*8, 9*). That is, the number of animals alive at any day postirradiation was used to calculate the cumulated number of animal days at risk (CAD), given by

$$\mathrm{CAD}_T = \sum_{i=1}^{i=T} N_i,$$

where N_i is the number of animals in the group that are alive on day i. The percentage incidence at time T is then given by

$$I_T = \frac{\text{incidence} \times 100}{\mathrm{CAD}_T}.$$

Four incidences have been calculated: animals with tumors, total number of tumors, adenocarcinomas, and fibroadenomas.

RESULTS

The general results obtained in the two experiments initiated in 1980–1981 (*1*) and in 1982–1983 differed in two important aspects. First, the proportion of adenocarcinomas observed in the control groups was appreciably higher in the second than in the first experiment, accounting for about 30% of all tumors in Experiment 1 controls and about 60% in Experiment 2 controls. This increase in the incidence of adenocarcinomas in Experiment 2 was less obvious in the irradiated groups (see below). Second, the mammary tumors appeared considerably earlier in the second than in the

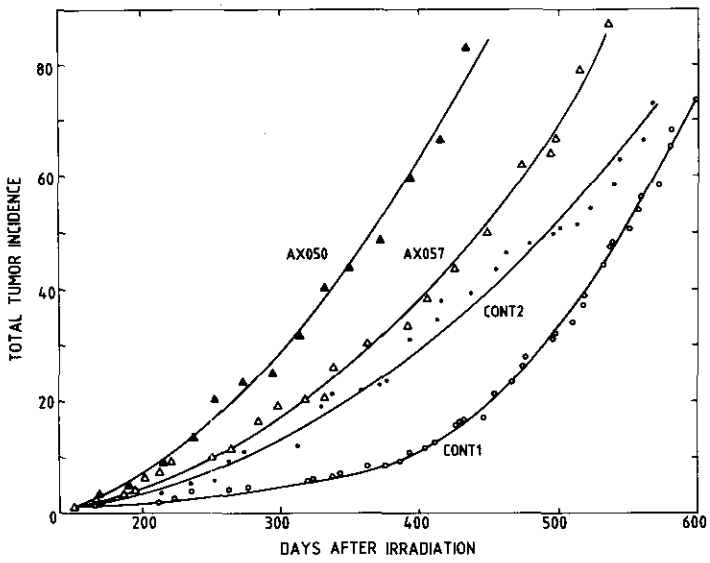

FIG. 1. Example of the time course of tumor incidence. There is a significant difference between the control animals in Experiments 1 (CONT1) and 2 (CONT2), as there is for animals receiving almost identical doses of acute X rays in Experiment 1 (AX057) and experiment 2 (AX050). The curves were obtained using the least-squares method to fit the data to a quadratic function.

first experiment (Fig. 1). This difference in time to tumor development was evident in both the control and irradiated groups, as shown for groups exposed to a similar dose of X rays in the two experiments (Fig. 1). In view of these differences, the γ and X irradiation results for the two experiments had to be analyzed separately. In addition, in many of the groups in Experiment 2 there was more than a 50% tumor incidence well before 450 days, which was used as the time for analysis in Experiment 1. Consequently, a shorter time (300 days) was used in the present analysis.

Data for the incidence against days after irradiation for each group of animals were fitted, using a least-squares method, to a quadratic function (see Fig. 1 for examples). These fits were then used to generate the results given in Tables II and III and the data points given in Figs. 2–4. A quadratic function is used in these analyses to obtain an adequate fit and does not necessarily imply anything about the underlying nature of the rate of increase of tumor incidence.

Figure 2A gives the time to achieve a 50% total tumor incidence as a function of dose for the three sets in Experiment 2, and demonstrates a different response of the chronic γ-irradiated groups compared to either the acute X- or acute γ-irradiated groups. Figures 2B and 2C give the time to achieve a 20% adenocarcinoma and fibroadenoma incidence. The 50% adenocarcinoma or fibroadenoma incidences were not used as these points are obtained from extrapolations beyond the time at which the experiment was terminated for most of the groups (see Table III). The lack of any dose-related change in the incidence of adenocarcinomas below the 2 Gy chronic γ dose (Fig. 2B) appears to be the main reason for the difference between chronic γ- and acute γ- and X-ray results shown in Fig. 2A.

TABLE II

Time in Days to Achieve the Indicated Percentage Incidence in Experiment 1

%	*CONT1*[a]	*HTO05*	*HTO10*	*HTO19*	*HTO44*	*CX029*	*CX057*	*CX110*	*CX200*	*AX057*	*AX178*	*AG064*	*CG093*
						(a) Incidence of animals with tumors							
10	389	301	233	195	157	266	254	237	185	252	139	304	376
20	464	382	135	260	205	351	334	318	246	332	203	381	443
30	522	442	385	309	243	436	393	379	294	394	254	439	494
40	569	492	444	349	275	521	443	430	335	446	297	488	537
50	612	535	495	385	304	606	486	474	371	493	335	530	575
						(b) Incidence of total tumors							
10	395	303	256	196	168	284	267	235	183	251	147	317	371
20	454	357	316	246	202	360	318	301	228	316	193	373	423
30	490	398	361	283	226	416	358	350	263	365	227	416	462
40	520	432	398	314	247	463	391	391	292	405	256	452	495
50	546	463	430	340	265	504	421	427	318	440	281	483	523
						(c) Incidence of adenocarcinomas							
10	492	387	373	240	190	404	368	342	217	357	176	425	506
20	570	487	484	333	259	556	471	473	314	464	283	500	583
30	630	562	565	401	311	(671)[b]	549	(569)	392	545	364	558	641
40	(681)	(624)	(632)	(457)	353	(768)	(615)	(648)	(458)	(613)	433	(608)	(691)
50	(726)	(679)	(691)	(505)	391	(853)	(672)	(717)	(516)	(673)	(494)	(651)	(734)
						(d) Incidence of fibroadenomas							
10	438	368	304	252	208	368	332	290	235	326	206	346	383
20	500	431	373	306	242	456	387	363	286	401	251	434	456
30	549	481	427	348	268	521	431	420	326	459	286	500	513
40	590	523	472	384	291	576	469	469	359	507	316	556	561
50	626	561	511	415	311	624	503	511	389	550	342	(605)	603

[a] Abbreviations as in Table I.

[b] Times in parentheses indicate that these results are extrapolations beyond the end of data for that particular group.

TABLE III

Time in Days to Achieve the Indicated Percentage Incidence in Experiment 2

%	*CONT2*[a]	*AX050*	*AX100*	*AX200*	*AX300*	*AG050*	*AG100*	*AG200*	*AG300*	*CG050*	*CG100*	*CG200*	*CG300*	*IG001*	*IG002*
						(a) Incidence of animals with tumors									
10	313	211	214	186	146	233	234	170	154	287	266	220	171	142	187
20	421	276	261	238	193	340	272	227	216	397	355	286	250	205	246
30	503	333	296	276	225	421	301	272	261	482	424	337	317	256	298
40	572	384	324	307	252	488	326	310	298	554	483	380	378	301	344
50	633	430	350	334	275	546	348	343	331	617	535	417	432	341	386
						(b) Incidence of total tumors									
10	273	216	209	180	144	237	239	177	148	257	240	239	173	167	187
20	346	267	242	217	180	305	264	215	187	328	305	278	224	209	230
30	403	305	267	243	204	354	283	243	219	390	354	308	265	240	263
40	451	338	288	264	224	395	300	267	243	444	396	333	299	264	290
50	494	366	306	282	241	430	314	288	265	494	433	355	330	286	315
						(c) Incidence of adenocarcinomas									
10	358	331	246	204	163	320	277	203	195	371	380	317	187	227	231
20	475	425	291	273	222	408	321	263	312	491	495	367	260	306	294
30	565	(495)	326	(322)	263	473	354	308	(400)[b]	(592)	(582)	406	317	364	342
40	(642)	(553)	355	(362)	296	527	(382)	346	(474)	(681)	(655)	439	367	(411)	382
50	(709)	(604)	(381)	(398)	(324)	(574)	(407)	(379)	(539)	(761)	(720)	(467)	410	(453)	418
						(d) Incidence of fibroadenomas									
10	463	250	264	233	196	314	263	230	193	308	304	267	268	197	234
20	579	315	309	273	230	406	296	280	230	453	405	333	353	245	297
30	(668)	365	343	304	256	477	321	318	258	577	483	383	421	282	346
40	(743)	408	372	(330)	278	537	343	351	282	(687)	550	425	479	313	388
50	(809)	445	(398)	(353)	298	(590)	363	(380)	304	(788)	(608)	(463)	(531)	340	424

[a] Abbreviations as in Table I.

[b] Times in parentheses indicate that these results are extrapolations beyond the end of data for that particular group.

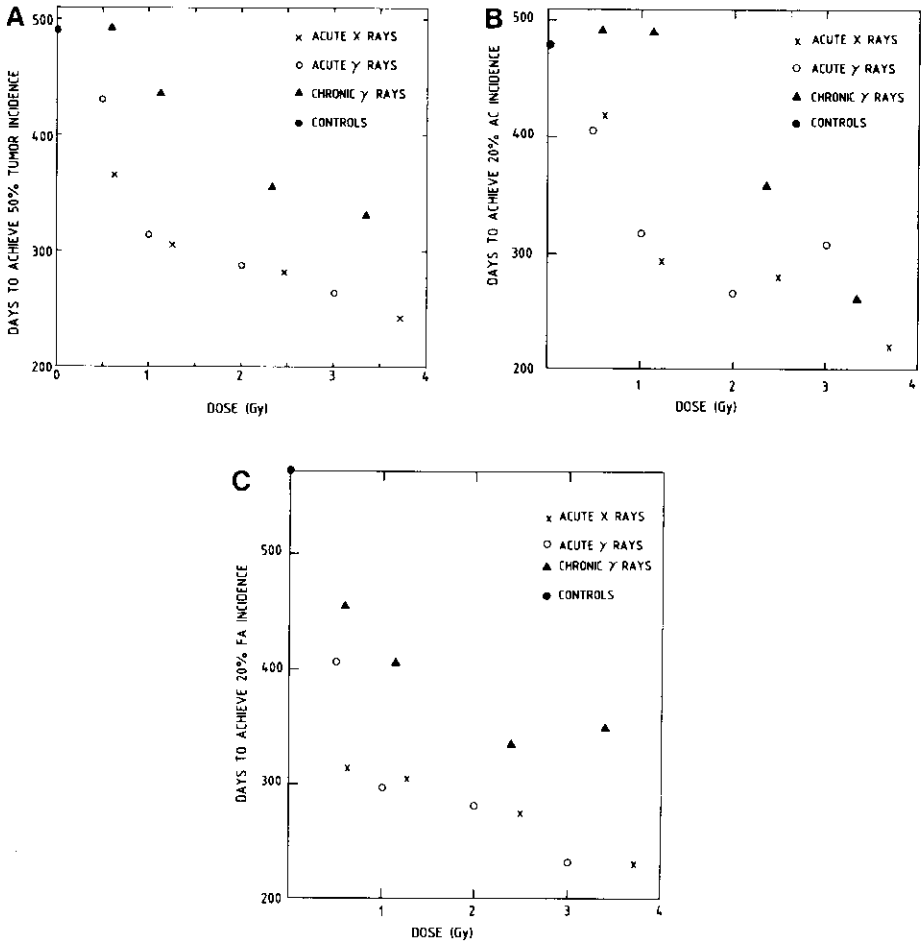

FIG. 2. Typical results for the time to reach a given tumor incidence in Experiment 2 (see Table III). The time to reach 50% total tumors (A) decreases rapidly with dose for acute X rays and γ rays to about 1 Gy and less rapidly after that. The decrease is significantly less rapid for chronic γ rays. The time to reach 20% adenocarcinomas (AC) (B) and fibroadenomas (FA) (C) indicates that the difference between chronic and acute γ irradiation is primarily due to the incidence of adenocarcinomas.

Tumor (total, adenocarcinoma, and fibroadenoma) incidence at 300 days as a function of dose for those groups of animals (see Table I) with more than one dose at the same dose rate are plotted in Fig. 3. The data were fitted by the least-squares method to a linear function (Fig. 3); the slopes and intercepts of the fits are given in Table IV. As can be seen in Fig. 3, and from the goodness of fit and R^2 values in Table IV, all of the sets of results are reasonably well fitted by a straight line except for the adenocarcinomas induced by γ irradiation. A linear response would describe the incidences of adenocarcinomas as a function of dose for both the acute and chronic irradiation groups if the data for 3 Gy and above were excluded. The 3.4 Gy result for chronic γ irradiations is considerably larger, and the 3 Gy result for acute γ irradi-

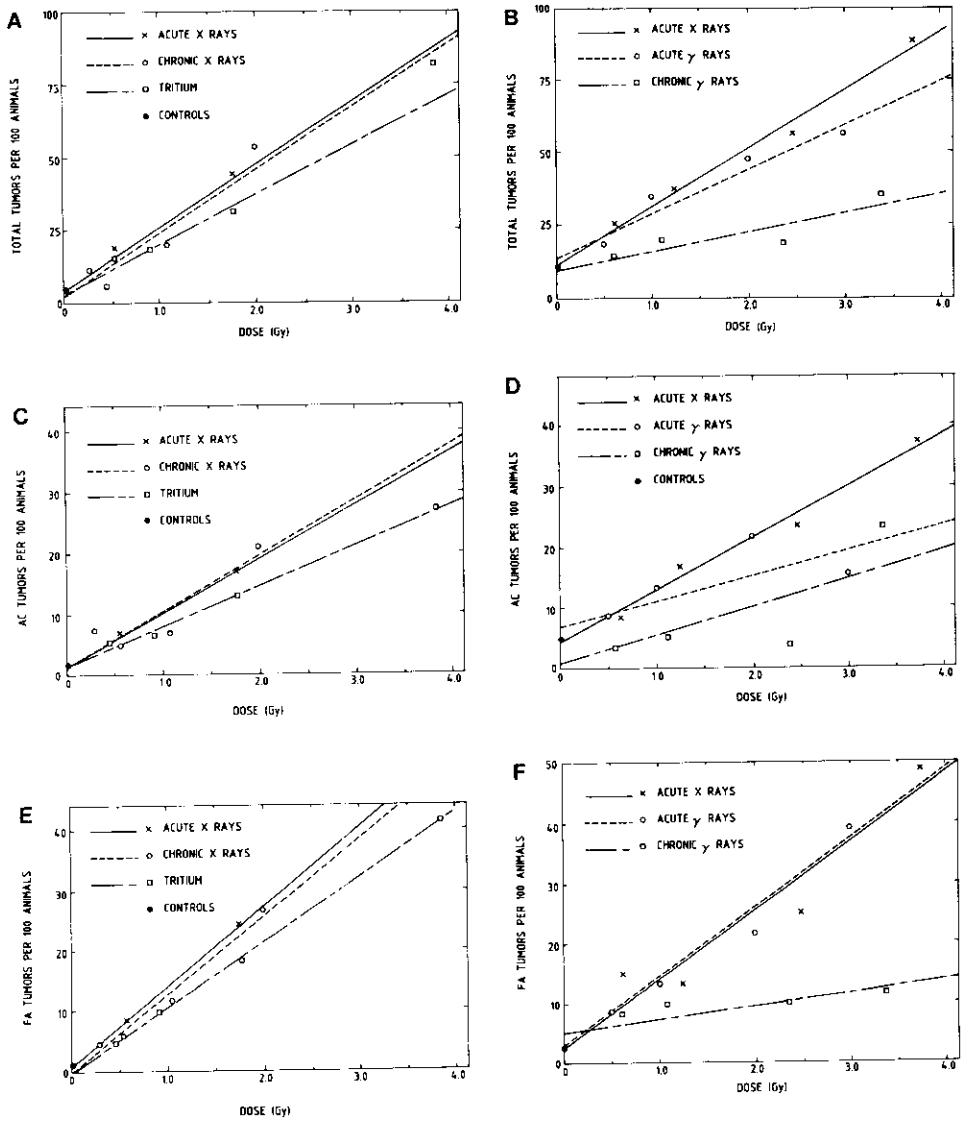

FIG. 3. Tumor incidence at 300 days as a function of dose for sets of animals in Experiments 1 and 2. A and B indicate incidence of all mammary tumors, C and D incidence of adenocarcinomas (AC), and E and F incidence of fibroadenomas (FA) per 100 animals at risk. A, C, and E are data from Experiment 1, while B, D, and F are data from Experiment 2. The lines are the results of linear least-squares fits. Uncertainties in the data points are approximately 20 and 30% at an incidence of 10 per 100 animals for Experiments 1 and 2, respectively, and about 15 and 20% at an incidence of 50 per 100 animals in Experiments 1 and 2, respectively.

ations smaller, than that which would be expected for a straight-line extrapolation from the data at lower doses (Fig. 3).

If the ratio of the slopes in Table IV is used as an estimate of the RBE as was done previously (*1*), it can be seen that the RBE for tritium (HTO) for incidence of total

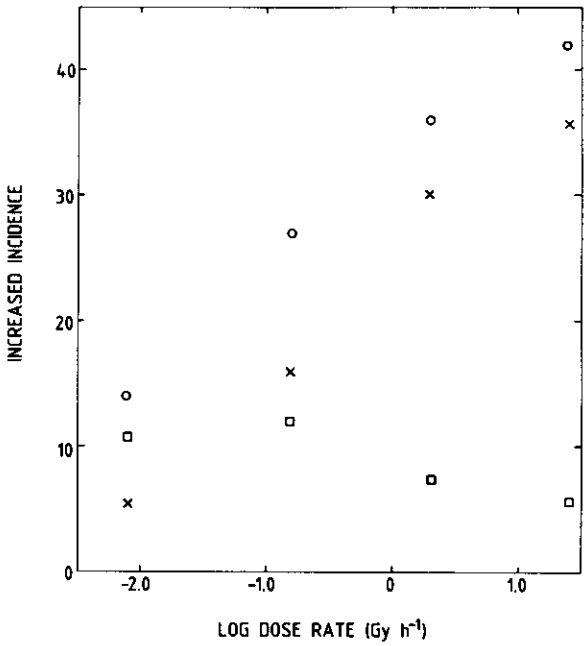

FIG. 4. Increase in incidence of mammary tumors at 300 days after exposure to 3 Gy ^{60}Co γ rays delivered at different dose rates in Experiment 2. (The lowest dose-rate points are for a dose of 3.35 Gy.) The control incidence has been subtracted. Uncertainties in the data points are approximately 30% at an excess incidence of 10 per 100 animals and 20% at an excess incidence of 40 per 100 animals. O, Total tumors; □, adenocarcinomas; ×, fibroadenomas.

tumors, adenocarcinomas, and fibrosarcomas is not significantly different from unity if chronic X ray is used as a standard (as indicated by the standard deviation of the slopes shown in Table IV). The slope for the acute X–ray data is slightly, but significantly, higher than that for tritium but is not different from the slopes for the chronic X–ray data (Table IV). Earlier results (*1*) at 450 days indicated that the slope for the acute X–ray response was significantly greater than that for the chronic X rays.

The results for chronic and acute γ irradiations are quite different, particularly at doses below 3 Gy (see Figs. 3B, 3D, and 3F). This is in contrast to the results for X rays where the responses to acute and chronic irradiation were similar (Fig. 3 and Table IV). If the comparison between acute X rays, acute γ rays, and chronic γ rays is restricted to the results below 3 Gy, then there is very good agreement between the response to acute X and acute γ rays; however, results for chronic γ rays cannot be distinguished from controls for total tumors, adenocarcinomas, and fibrosarcomas (see Fig. 3). This same conclusion can be drawn for the fibroadenomas when the results for 3 Gy and above are included (Fig. 3F), but the data for adenocarcinomas were completely different (Fig. 3D) as noted above.

The different response of adenocarcinomas and fibroadenomas with dose rate at high total doses of γ rays is shown in more detail in Fig. 4, which includes the incidence for the intermediate dose–rate groups (see Table I). The increase in the inci-

TABLE IV

Slopes and Zero Dose Intercepts for the Linear Least-Squares Fits Shown in Fig. 3

Set	*Control incidence*	*Calculated intercept*	*Calculated slope*	*Goodness of fit*	R^2
		Total tumors per 100 animals			
HTO[a]	4.6	4.0 ± 1.4[b]	16.8 ± 0.5	0.2	1.0
CX	4.6	3.4 ± 5.0	21.3 ± 3.2	1.4	0.94
AX1	4.6	5.6 ± 1.9	21.4 ± 1.5	0.3	1.0
AX2	10.9	11.3 ± 3.6	20.0 ± 1.2	1.0	0.99
AG	10.9	13.7 ± 5.1	15.2 ± 2.1	1.4	0.95
CG	10.9	10.2 ± 4.7	6.3 ± 1.7	2.8	0.81
		Adenocarcinomas per 100 animals			
HTO	1.5	1.5 ± 0.9	6.6 ± 0.3	0.2	0.99
CX	1.5	1.2 ± 3.3	8.8 ± 2.1	1.4	0.85
AX1	1.5	1.6 ± 0.2	8.7 ± 0.1	0.1	1.0
AX2	5.0	4.4 ± 2.0	8.6 ± 0.7	0.5	0.98
AG	5.0	7.4 ± 4.8	4.1 ± 2.0	1.3	0.59
CG	5.0	1.1 ± 6.8	4.7 ± 2.5	5.9	0.54
		Fibroadenomas per 100 animals			
HTO	1.0	0.2 ± 0.7	10.6 ± 0.2	1.3	1.0
CX	1.0	−0.2 ± 1.8	12.9 ± 1.2	0.8	0.98
AX1	1.0	1.0 ± 0.1	13.1 ± 0.1	0.1	1.0
AX2	2.5	2.7 ± 5.4	11.4 ± 1.8	1.6	0.93
AG	2.5	3.7 ± 4.1	11.3 ± 1.7	1.2	0.94
CG	2.5	5.4 ± 2.4	2.1 ± 6.9	2.0	0.66

[a] Abbreviations as in Table I.

[b] Standard deviations of the estimate of the slope and intercepts obtained by the least-squares method. The actual incidences in the control groups are included for ease of comparison. The goodness of fit (χ^2/degrees of freedom) parameter and the R^2 statistic are given for each fit.

dence in fibroadenomas as a function of the dose rate is approximately linear, rising by a factor of about 6 with the increase in dose rate from 0.0076 to 2.63 Gy h^{-1}, while the adenocarcinomas do not increase with dose rate (Fig. 4). These γ dose–rate results are at a relatively high total dose of 3 Gy (3.4 Gy for the lowest dose rate). Unfortunately, no results for intermediate dose rates are available in Experiment 2 at lower doses (2 Gy and below) where the response for adenocarcinomas appears linear with dose for the acute γ-ray exposures (see Fig. 3D), and where there appears to be a significant dose–rate effect. Data from Experiment 1 do support a dose-rate effect for adenocarcinomas at lower doses; the incidence of adenocarcinomas was less than controls for 0.93 Gy γ rays at 0.002 Gy h^{-1}, but greater than controls for 0.64 Gy γ rays at 0.6 Gy h^{-1} (Table II).

DISCUSSION AND CONCLUSIONS

A puzzling feature of these results is the difference in ratio of adenocarcinomas and fibroadenomas in control animals in the two experiments. For example, when the

incidence of adenocarcinomas in control animals had reached 30%, the incidence of fibroadenomas was slightly greater than 50% in Experiment 1 (Table II) but just under 20% in Experiment 2 (Table III). The ratios observed in Experiment 1 are closer to those reported by previous investigators (*2*).

A simple explanation for the differences in incidences of adenocarcinomas obtained for the control groups in the two experiments (Tables II–IV) carried out in this laboratory 2 years apart is not apparent. Animals of the same strain and similar age were obtained from the same supplier and held in the same animal facility under essentially the same conditions; moreover, the histological classification of mammary tumors from the two experiments was carried out by the same person at about the same time. It is known that female rats of different strains exhibit large inherited differences in susceptibility to induction of mammary tumors by radiation (*12–16*); appreciable differences have also been observed in the same laboratory between rats of the same nominal strain which were obtained from different suppliers (*20*). The appearance of mammary tumors in both control and irradiated female rats is known to be highly dependent on levels of certain pituitary and ovarian hormones (*15–19*). Further, the inductions of fibroadenomas and adenocarcinomas appear to be independent phenomena because there is no significant relationship between the incidence of these two types of mammary tumors in female rats (*21*). It is possible that the apparently similar animals used in the two experiments in our laboratory were not actually genetically or physiologically homogeneous. Alternatively, there may have been changes in the diet that affected the spontaneous rate even though the same rat chow from the same supplier was used in both experiments. However, these differences did not appear to have a major effect on the dose–response curves observed at 300 days after irradiation (Fig. 3).

The data from the two experiments with female Sprague–Dawley rats were consistent in showing that the yield of all mammary tumors after exposure to tritium, chronic and acute X rays, and acute γ rays was compatible with a linear dose–response relationship and was significantly reduced when the dose rate was reduced for γ irradiation for doses below 3 Gy (Fig. 3). There was, moreover, little difference in the yield of all mammary tumors per unit dose for acute X rays, chronic X rays, tritium β rays, and acute γ rays (Figs. 2 and 3; Table IV). The apparent RBE of 0.8 for tritium β rays compared to chronic X rays at 300 days after irradiation (Table IV) agrees with the data presented in our previous report (see Figs. 5 and 6 in Ref. (*1*)). More detailed analyses of these data suggested, however, that the best value of the RBE for tritium β rays compared to chronic X rays was in the region of 1.0–1.3 (*1*). The tritium RBE values appear to be close to unity for yields of all mammary tumors and of fibroadenomas and adenocarcinomas (Fig. 3; Table IV).

The present data suggest that reduction of the dose rate has a larger effect on yield of all mammary tumors per unit dose for γ rays than it does on yield for X rays (Fig. 3; Table IV). This general result is consistent with data from other experiments using non-cancer end points (*22, 23*). The dose-rate effectiveness factor (*6*) with γ rays at 300 days after irradiation in our study was in the range of 2.4 (Table IV) to 3 (Fig. 4). Similar values can be derived from the results given in two previous publications dealing with yield of all mammary tumors after protraction or fractionation of γ-ray doses (*2, 5*), while the dose–rate effectiveness factor for protracted or fractionated X

rays would appear from previous publications to be somewhere in the region of 1 to 1.7 (*1, 4, 24*). However, there is no guarantee that the yield of mammary tumors has reached a minimum at the lowest chronic γ dose rate used in the present study (Fig. 4).

The data for fibroadenomas tended to follow the same general pattern as those for all mammary tumors. The dose-rate effectiveness factor (*6*) with γ rays appeared to be in the region of 5–6 for the yield of fibroadenomas at 300 days after irradiation (Table III; Fig. 4) but somewhat smaller for the decrease in time to development of 0.2 fibroadenomas per animal at risk (Fig. 2). The data for adenocarcinomas following either acute or chronic γ radiation were complicated by unexpected apparent deviations from a linear dose–response relationship at cumulative doses of 3 Gy or more (Fig. 3), with no reduction in incidence of adenocarcinomas due to dose protraction at a total dose in the region of 3 Gy (Table III; Figs. 3 and 4). It is, however, of interest to note that no increase in incidence of adenocarcinomas was observed in three groups with chronic γ radiation at doses of 0.59, 0.93, and 1.1 Gy at dose rates of 0.002–0.0076 Gy h^{-1} (Tables II and III; Figs. 2 and 3).

In summary, the results of these two experiments are as follows:

The incidence of all tumors at a given time was linear with dose for all groups except the adenocarcinomas from γ-ray exposures. The incidence of adenocarcinomas for acute γ irradiation was linear with dose to 2 Gy, but less than expected based on a linear dose–response relationship for the results at 3 Gy.

No significant increase in adenocarcinomas above controls was observed at 1.1 Gy and below with chronic γ radiation.

The incidence of all tumors and of fibroadenomas increased almost linearly with the log of dose rate in the range 0.0076 to 26.3 Gy h^{-1} for 3 Gy doses of ^{60}Co γ rays (Fig. 4). The results with X rays did not demonstrate a significant dose-rate effect at 300 days for any tumor type (Fig. 3), although the results at 450 days did exhibit a small dose-rate effect (*1*). Adenocarcinomas at 3.0 Gy did not exhibit a dose-rate effect for γ rays (Fig. 4), but results at lower doses from both experiments support a dose-rate effect similar to that found for fibroadenomas.

The data do not appear to support a relative risk model for the induction of adenocarcinomas. The control incidence at 300 days after irradiation increased by a factor of three between Experiments 1 and 2, and there was no corresponding increase in the yield per unit dose (Table IV).

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