3. Studies of Cancer in Experimental Animals

Neutrons have been studied in order to compare their carcinogenicity with that of low-LET radiations such as X-radiation and γ-radiation, not only to improve understanding of the risks of exposure to neutrons but also to test biophysical models and their applicability to radiation-induced cancer. This section does not give a comprehensive presentation of all studies in animals. The studies in mice summarized below are those which have provided data on dose–response relationships and on the effects of fractionation and dose rate at low doses of neutrons. The results of experiments in other species provide evidence that the results in mice are not unique.

3.1 Adult animals

3.1.1 *Mouse*

Groups of 21–114 male and 31–197 female non-inbred RF/Un mice, 10 weeks of age, were exposed to 0–9.3 Gy of whole-body irradiation with 1-MeV or 5-MeV neutrons [source and γ-radiation component not specified] at dose rates of 0.04–114 mGy day^{-1} and 0.00003–850 mGy min^{-1}. The animals were allowed to die naturally or were killed when moribund, at which time all animals were necropsied. Only selected lesions were examined histopathologically, as needed, to confirm diagnosis. In the control group of 301 unirradiated females and 115 unirradiated males, neoplasms occurred in about 64% of females and 47% of males. The incidence of myeloid leukaemia was markedly increased by acute exposure, passing through a maximum at 2 Gy and declining at higher doses (Table 5). Chronic irradiation at up to 5.7 Gy also enhanced the incidence, but this declined after exposure to 9.3 Gy. The incidence of reticulum-cell neoplasms, in contrast to those of myeloid leukaemia and thymic lymphoma, decreased with the increased doses delivered at a high rate. Of the unirradiated control mice, 11–14% had pulmonary tumours (adenomas); in treated mice, however, the incidences decreased with increasing dose. The incidence of ovarian tumours (granulosa-cell tumours, luteomas, tubular adenomas and haemangiomas) was statistically significantly increased ($p < 0.05$) only at the lowest dose of 16 mGy at a rate of 0.00003 mGy min^{-1} [statistical method not specified]. The incidences of solid tumours other than of the lung and ovary were increased in the irradiated animals, but the numbers were reported to be insufficient to establish a quantitative dose–effect relationship. The relative biological effectiveness (RBE; see section 1.2) for the induction of myeloid leukaemia was 16 with daily and chronic exposure as

Table 5. Time to death and incidences of tumours in various organs of RF/Un mice exposed to fast neutrons

Mean accumulated dose (Gy)	Average dose rate (mGy min^{-1})	No. of mice	Mean age at death (days)	Myeloid leukaemia (%)	Thymic lymphoma (%)	Ovarian tumours (%)	Pulmonary tumours (%)	Other solid tumours (%)
Females								
0	–	301	582	3	12	2	11	3
0.016	0.00003	111	584	5	11	19	15	4
0.12	0.00021	97	549	8	11	2	10	1
0.15	0.0015	79	558	6	9	4	13	2
0.16	0.00022	99	566	7	7	4	11	3
0.16	0.0007	117	558	3	8	5	14	4
0.27	0.0004	129	549	4	12	1	12	2
0.28	0.033	50	533	4	8	0	12	2
0.30	0.0062	100	544	8	11	4	15	4
0.31	0.0012	148	578	4	11	2	17	4
0.33	0.0043	90	522	8	19	4	4	3
0.68	0.0037	60	523	7	10	9	17	0
0.75	0.0034	120	471	9	21	2	12	7
0.94	0.0062	197	464	12	19	3	14	4
0.96	0.0099	49	509	5	27	14	5	5
0.98	0.033	85	464	15	20	5	7	4
1.69	0.0033	123	489	14	12	6	17	4
2.10	0.0185	50	451	15	41	4	7	2
2.11	0.0099	49	370	8	39	2	8	0
2.39	0.0275	58	324	20	25	2	4	0
2.91	0.0171	49	431	9	40	9	13	4
3.90	0.0098	120	398	17	35	1	10	3
4.61	0.0207	186	301	12	45	2	6	2
5.70	0.0185	50	363	23	25	0	16	0
9.30	0.083	50	189	2	20	0	2	0

Table 5 (contd)

Mean accumulated dose (Gy)	Average dose rate (mGy min^{-1})	No. of mice	Mean age at death (days)	Myeloid leukaemia (%)	Thymic lymphoma (%)	Ovarian tumours (%)	Pulmonary tumours (%)	Other solid tumours (%)
Females (contd)								
2.03	850	31	382	20	23	10	0	0
2.60	850	60	304	16	10	7	4	0
3.60	850	98	360	10	23	8	4	2
4.43	850	82	342	9	16	7	2	1
Males								
0	–	115	548	3	1		14	2
0.17	0.0012	77	561	8	1		17	1
0.29	0.0029	69	482	17	1		17	1
1.20	0.0243	21	502	29	5		19	5
1.30	850	27	460	33	7		11	0
1.72	850	48	436	34	11		11	2
2.22	850	114	428	38	4		7	1
2.70	850	103	413	30	5		8	3
3.32	850	79	408	23	9		13	4

From Upton *et al*. (1970)

compared with acute exposure (Upton *et al.*, 1970). [The Working Group noted that the tumour incidences were not analysed for competing causes of death. Since a large fraction of the irradiated mice died early from myeloid leukaemia, such an analysis for solid tumours is essential.]

A total of 3265 female RFM/Un mice, 12 weeks of age, received whole-body irradiation with neutrons at doses of 0.048, 0.096, 0.192, 0.24, 0.47, 0.94 or 1.88 Gy at rates of 50 or 250 mGy min^{-1} or 10 mGy day^{-1}. A reactor was used to deliver the high dose rate, and the low dose rate was produced from a 1.1-mg ^{252}Cf source surrounded by a depleted ^{238}U sphere (Storer *et al.*, 1979). The ratios of neutrons:γ-rays were 7:1 for the reactor and 3:1 for the ^{252}Cf source. A control group of 648 mice was available. The animals were followed for life, and tumours were diagnosed histologically. A positive dose–response relationship for thymic lymphoma was observed at all doses up to 1.0 Gy at both dose rates; at the highest dose, the low dose rate was more effective (Table 6). At low doses, a weak dependence on rate was observed. Increased incidences of thymic lymphoma, lung adenoma and endocrine tumours were seen at doses as low as 0.24 Gy. The highest dose of radiation at the low rate (10 mGy day^{-1}) appeared to induce thymic lymphomas more efficiently than irradiation at the high dose rate (250 mGy min^{-1}). The incidence of ovarian tumours was lower at all doses given at the low rate than at the high rate. After exposure to doses of 0.24–0.47 Gy, the RBE for thymic lymphoma was 3–4 in relation to acute exposure to ^{137}Cs γ-rays, and the induction of mammary tumours also appeared to be more sensitive to neutrons; however, no apparent effect of dose or dose rate was reported over the dose range used. Because of the relatively large carcinogenic effect, the authors concluded that the γ-radiation component had little or no effect on the dose–response relationship observed (Ullrich *et al.*, 1976).

The dose–response relationships for the induction of lung tumours were studied in 592 female RFM/Un mice, 10–12 weeks of age, given thoracic exposure to 0.05–1.5 Gy of fission neutrons at a rate of 50–250 mGy min^{-1} and compared with 88 controls. When the mice were killed nine months after irradiation, the relationship between the number of lung tumours per mouse and doses up to 0.25 Gy was linear, or a threshold model with a linear response above the threshold was reported. The RBE increased with decreasing dose from 25 at 0.25 Gy to 40 at 0.10 Gy in relation to acute exposure to X-rays (Ullrich *et al.*, 1979). In another study (Ullrich, 1980), mice of the same strain were irradiated with 0, 0.1, 0.15, 0.2, 0.5, 1.0 or 1.5 Gy as either single doses or two equal doses separated by 24-h or 30-day intervals. The animals were observed until nine months of age. Dose fractionation had no effect on lung tumour induction at any dose.

In a study with female BALB/c/AnNBd mice, 296 control and 3258 irradiated mice, 12 weeks of age, received whole-body exposure to fission spectrum neutrons at doses of 0, 0.048, 0.096, 0.192, 0.24, 0.47, 0. 94 or 1.88 Gy at a dose rate of 50 or 250 mGy min^{-1} or 10 mGy day^{-1}. The animals were observed for life, and the induced tumours were examined histologically. The tumours that were most sensitive to induction by neutrons

Table 6. Incidences of neoplasms in female RFM/Un mice after neutron irradiation at various doses and rates

Dose rate	Type of neoplasm	Incidence (%)				
		0	0.048 Gy	0.096 Gy	0.192 Gy	0.47 Gy
50 mGy min^{-1}	Thymic lymphoma	7.3	11	11	20	33
	Lung adenoma	24	10	24	30	46
	Endocrine tumours	7.0	5.2	11	50	54
		0	0.24 Gy	0.47 Gy	0.94 Gy	1.88 Gy
250 mGy min^{-1}	Thymic lymphoma	4.6	24	30	40	39
	Reticulum-cell sarcoma	62	53	53	52	31
	Myeloid leukaemia	0	0.56	5.3	1.3	0.62
	Other leukaemias	6.4	6.9	7.5	7.7	9.6
	Lung adenoma	31	42	45	53	16
	Ovarian tumours	0	20	25	52	39
	Pituitary tumours	3.9	7.9	29	21	16
	Harderian gland tumours	0	13	28	35	6.3
	Uterine tumours	1.3	11	25	27	19
	Mammary tumours	2.6	8.0	8.4	10	3.9
	Other solid tumours	3.9	14	24	20	26
10 mGy day^{-1}	Thymic lymphoma	–	18	25	43	63
	Reticulum-cell sarcoma	–	64	58	48	45
	Myeloid leukaemia	–	0	2.4	0.27	0.26
	Other leukaemias	–	4.4	2.9	3.1	4.2
	Lung adenoma	–	48	48	53	32
	Ovarian tumours	–	2.3	8.7	22	24
	Pituitary tumours	–	11	11	19	2.5
	Harderian gland tumours	–	11	20	25	4.5
	Uterine tumours	–	4.8	17	21	18
	Mammary tumours	–	7.3	7.6	5.4	8.9
	Other solid tumours	–	21	14	21	12

From Ullrich *et al.* (1976)

were malignant lung adenocarcinomas, mammary adenocarcinomas and ovarian tumours, and increases in the incidences of these three types of tumours were observed after exposure to doses of neutrons as low as 50–100 mGy at a high dose rate (Table 7; Ullrich *et al*., 1977).

Groups of 140–182 female BALB/c/AnNBd mice, 12 weeks of age, received a single whole-body exposure to 0.025, 0.05, 0.10, 0.20, 0.50 or 2.0 Gy of fission neutrons at a dose rate of 50–250 mGy min^{-1}. The animals were studied for life, and tumours were examined histologically. A group of 263 controls was available. The ovary was very sensitive to the induction of tumours (granulosa-cell tumours, luteomas

Table 7. Incidences of leukaemias and solid tumours in neutron-irradiated female BALB/c mice

Dose rate	Dose (Gy)	Thymic lymphoma (%)	Reticulum-cell sarcoma (%)	Lung adenoma (%)	Lung adenocarcinoma (%)	Mammary tumours (%)	Ovarian tumours (%)
Control	0	1.1 ± 0.6	41 ± 4.1	26 ± 4.5	13 ± 3.4	7 ± 1.6	6 ± 2.1
50 mGy min^{-1}	0.048	1.0 ± 0.9	39 ± 6.6	11 ± 5.4	27 ± 4.8	7 ± 2.6	7 ± 4.1
	0.096	2.1 ± 1.4	32 ± 6.5	13 ± 6.2	39 ± 5.1	25 ± 4.5	11 ± 4.6
	0.192	2.2 ± 1.6	30 ± 5.8	17 ± 4.9	19 ± 5.1	18 ± 5.0	20 ± 4.9
	0.47	2.8 ± 1.7	27 ± 4.6	28 ± 4.6	22 ± 4.7	17 ± 5.6	49 ± 4.0
250 mGy min^{-1}	0.24	1.8 ± 0.8	29 ± 4.6	25 ± 4.5	19 ± 4.8	17 ± 2.4	37 ± 4.6
	0.47	2.4 ± 0.7	32 ± 6.4	27 ± 5.4	23 ± 5.1	19 ± 3.7	57 ± 5.4
	0.94	4.1 ± 1.3	26 ± 5.4	30 ± 4.9	19 ± 5.7	17 ± 3.9	62 ± 3.5
	1.88	4.5 ± 1.2	21 ± 3.6	23 ± 3.3	13 ± 5.2	15 ± 5.4	39 ± 5.5
10 mGy day^{-1}	0.24	2.1 ± 1.2	38 ± 4.5	28 ± 5.1	13 ± 4.6	14 ± 2.9	7 ± 2.9
	0.47	2.3 ± 0.9	36 ± 4.8	23 ± 5.1	27 ± 5.7	17 ± 3.7	10 ± 3.7
	0.94	2.9 ± 1.0	36 ± 4.1	22 ± 4.0	32 ± 5.5	19 ± 3.8	19 ± 4.2
	1.88	6.1 ± 1.6	28 ± 6.2	13 ± 2.6	43 ± 5.7	45 ± 5.3	21 ± 5.1

From Ullrich *et al*. (1977); incidences are means ± SE.

and tubular adenomas), the incidence increasing from 2% in controls to 76% after exposure to 0.50 Gy; at 2.0 Gy, the incidence was 56%. For mammary adenocarcinomas, a linear dose–response relationship was reported up to a dose of 0.50 Gy, from 8% in controls to 25%. For lung adenocarcinomas, a convex upward curve was seen over the dose range 0–0.50 Gy. In the dose range 0.1–0.2 Gy, the dose–response curve for the induction of lung and mammary tumours appeared to 'bend over'. The percentage incidences of lung and mammary adenocarcinomas and ovarian tumours are given in Table 8 (Ullrich, 1983).

Table 8. Incidences of solid tumours in female BALB/c mice after fission neutron irradiation

Dose (Gy)	No. of animals	Lung adenocarcinoma (%)	Mammary adenocarcinoma (%)	Ovarian tumours (%)
0	263	15 ± 2.4	8 ± 1.7	2 ± 1.0
0.025	140	17 ± 3.7	11 ± 2.9	3 ± 1.4
0.05	160	21 ± 4.3	17 ± 3.8	7 ± 2.1
0.10	160	18 ± 4.0	18 ± 4.2	10 ± 2.6
0.20	167	30. ± 6.1	20 ± 4.7	16 ± 3.7
0.50	182	37 ± 6.9	25 ± 5.5	76 ± 3.0
2.0	182	27 ± 6.1	8 ± 3.2	56 ± 3.8

From Ullrich (1983); incidences are means ± SE.

In the same model, the effects of dose rate and of dose fractionation on the carcinogenic effects of fission spectrum neutrons were examined for doses of 0, 0.025, 0.05, 0.10, 0.20 or 0.50 Gy in 263 controls and 140–191 animals in the various irradiated groups. Whole-body irradiation was given as a single dose or split at 24-h or 30-day intervals at dose rates of 10–250 mGy min^{-1}, depending on the total dose. The incidence of ovarian tumours was not altered by fractionation, but lowering the dose rate reduced the incidence of ovarian tumours and enhanced the frequency of mammary tumours at doses as low as 0.025 Gy (Ullrich, 1984).

A total of 1814 male RFM/Un mice, 10 weeks of age, were exposed by whole-body irradiation to 0.05, 0.1, 0.2, 0.4 or 0.8 Gy of fission neutrons at a rate of 0.25 Gy min^{-1}. The radiation facility was the same as that used in previous studies. A group of 602 controls was available. The lifetime incidence of myeloid leukaemia was increased in a dose-related manner from 0.8 ± 0.4 in controls to 2.1 ± 0.5 at 0.05 Gy, 2.6 ± 0.7 at 0.1 Gy, 4.8 ± 1.3 at 0.2 Gy, 7.5 ± 2.2 at 0.4 Gy and 14.9 ± 3.8% at 0.8 Gy. In comparison with acute ^{137}Cs γ-radiation, the RBE for myeloid leukaemia was 2.8 (Ullrich & Preston, 1987).

Radiation-induced late somatic effects and the shapes of the dose–response curves after graded doses of 1.5-MeV fission neutrons at 0.17, 0.36, 0.71, 1.07, 1.43, 1.79 or

2.14 Gy were reported in 360 male $BC3F_1$ [(C57BL/Cne × C3H/HeCne) F_1] mice, three months of age, after whole-body irradiation. The γ-ray component represented about 12.5% of the total dose. A control group of 561 male mice was available. A significant decrease in the mean life span was observed at 0.36 Gy and with increasing doses from 1.07 to 2.14 Gy ($p < 0.001$, Student's *t* test). Myeloid leukaemia, malignant lymphoma and solid tumours including cancers of the lung, liver and soft tissues were observed. A significant increase in the incidence of myeloid leukaemia was reported at doses of 0.71 to 1.79 Gy ($p < 0.001$, χ^2 test) when compared with controls (0%). A significant decrease in the incidence of malignant lymphoma was observed after exposure to 1.43–2.14 Gy. The incidences of solid tumours were significantly ($p < 0.05$) increased even at doses of 0.36–1.79 Gy when compared with controls (31%). The incidence of myeloid leukaemia fit a curvilinear model, and the RBE at the lowest dose of 0.17 Gy was about 4 with reference to an acute dose of 250-kVp X-rays (Covelli *et al*., 1989).

The thoraxes of 474 male and 464 female SAS/4 albino outbred mice, three months of age, were exposed locally to 0.10, 0.25, 0.5, 0.75, 1, 2, 3 or 4 Gy of fast neutrons (mean energy, 7.5 MeV, with 3% γ-rays, beryllium target) at a rate of 1.06 Gy min^{-1}; the rest of the body was shielded. At the time of irradiation, the mice were anaesthetized with 57 mg $(kg\ bw)^{-1}$ sodium pentobarbitone. A group of 219 male and 210 female controls was available. After 12 months of irradiation, the animals were necropsied. Histologically, the lung tumours appeared to be a mixture of benign encapsulated adenomas and malignant invasive adenocarcinomas. The dose–response curve for animals of each sex was 'bell shaped' and steeply linear up to 1 Gy, peaked between 1 and 3 Gy and sharply declined at 4 Gy. In females, the incidences of lung tumours were 9% at 0 Gy (control) and 17.5, 24.1, 25.5, 27.9, 30.5, 33.9, 29.5 and 15.5% at the respective doses; in males, the percentage incidences were 16.5 (controls), 28.3, 32.7, 27.6, 29.1, 41.5, 42.2, 44.9 and 20.0%, respectively. The RBE for doses < 1 Gy of neutrons in comparison with < 3 Gy of 200-kVp acute X-ray exposure was 7.1 for females and 4.5 for males (Coggle, 1988).

Groups of 60 female (C57BL/6N × C3H/He) F_1 ($B6C3F_1$) mice, seven to eight weeks of age, were exposed by whole-body irradiation to a dose of 0.27 Gy at 0.059 mGy min^{-1} or 2.7 Gy at 0.53 mGy min^{-1} from ^{252}Cf fission neutrons (mean energy, 2.13 MeV; 35% γ-ray contamination). A group of 60 age-matched females was used as controls. The carcinogenic effects were examined 750 days after irradiation by gross observation and histopathologically. Both doses induced significantly higher incidences of neoplasms in the ovary, pituitary gland, Harderian gland, liver, mammary gland and reticulum cells (at 2.7 Gy only) and of lipoma (at 0.27 Gy only) (χ^2 test). No RBE was reported. There was no significant increase in the incidences of tumours in the lung, uterus and vagina, adrenal gland, soft tissue, bone, pancreas, stomach or thyroid gland, or of haemangiosarcoma or leukaemia after exposure to 0.27 or 2.7 Gy. More frequent development of multiple tumours was reported in the

neutron-irradiated animals in comparison with animals exposed to γ-rays (^{60}Co, ^{137}Cs) (Seyama *et al*., 1991).

In a study of the influences of strain and sex on the development of tumours, 190 male and 151 female B6C3F$_1$ hybrid (C57BL × C3H), 65 male and 60 female C3B6F$_1$, 117 male and 112 female C57BL/6N and 156 male and 139 female C3H/HeN mice, six weeks of age, were exposed by whole-body irradiation to 0 (control), 0.125, 0.5 or 2 Gy of ^{252}Cf neutrons at a rate of 6–8 mGy min^{-1} (mean energy, 2.13 MeV; γ-ray component, 35%) and were observed up to 13 months of age. Tumours were identified histopathologically. The total tumour incidence was high in C3H/HeN, moderate in B6C3F$_1$ and C3B6F$_1$ and low in C57BL/6N mice (Table 9) because of high frequencies of liver tumours in males and ovarian tumours in females. A dose-dependent increase in liver tumours was reported in both males and females of all strains but the increase was greater in males than in females. Ovarian tumours were more frequent in C3H/HeN mice, followed by B6C3F$_1$, C3B6F$_1$ and C57BL/6N. Of the strains and hybrids, B6C3F$_1$, C57BL/6N and C3H/HeN were the most sensitive to low doses around 0.50 Gy (Ito *et al*., 1992; Takahashi *et al*., 1992).

In a series of experiments during the period 1971–86, thousands of male and female B6C3F$_1$ mice were exposed by whole-body irradiation to single or fractionated doses of fission neutrons. The effects on survival were reported by Ainsworth *et al*. (1975), Thomson *et al*. (1985a,b, 1986) and Thomson and Grahn (1988). In a report on tumour induction, several thousand male and female B6CF$_1$ (C57BL/6 × BALB/c) mice, 110 ± 7 days of age, were exposed to 0–2.4 Gy of fission neutrons, as single doses, 24 equal doses once weekly or 60 equal doses once weekly. The mean energy was 0.85 MeV; 2.5% of the dose was due to γ-radiation and 0.1% was thermal neutrons. A total of 901 age-matched males and 1199 age-matched females were used as controls. All the mice were followed for life, and the tumours were identified histopathologically. Most of those found in both control and irradiated mice were lymphoreticular, vascular and pulmonary tumours. About 85% of the irradiated mice died with or from one or more neoplasms. Dose-dependent increases in the incidence of lymphoreticular, lung, liver, Harderian gland and ovarian tumours were observed. The connective tissues showed less sensitivity to radiation-induced cancers than epithelial tissues, and the latter showed RBE values of 75 or greater with reference to chronic exposure to γ-rays (Grahn *et al*., 1992).

A total of 742 male BC3F$_1$ mice, three months of age, were exposed to five equal daily fractions of fission neutrons with a mean neutron energy of 4 MeV and a 12% γ-ray component, to yield cumulative doses of 0.025, 0.05, 0.1, 0.17, 0.25, 0.36, 0.535 and 0.71 Gy, given at a rate of 4 mGy min^{-1}. A group of 193 controls was available. The animals were kept for life, and tumours were examined grossly and histopathologically. The incidence of myeloid leukaemia showed a significant positive trend (Peto's test) at doses of 0–0.17 Gy and up to 0.36 Gy. The incidence of epithelial tumours was increased significantly ($p < 0.001$) at doses from 0.17 Gy, those of liver and lung tumours at doses from 0.025 Gy, that of skin tumours from 0.36 Gy and that

Table 9. Strain and sex differences in the incidence of ^{252}Cf neutron-induced tumours in mice

Reference	Dose (Gy)	Strain and sex	Effective no. of mice	Survival rate (%)	Liver tumours (%)	Lymphoma (%)	Adrenal tumours (%)	Ovarian tumours (%)
Ito *et al*. (1992)		C57BL/6N Male						
	0		23	82	0	0	0	
	0.125		32	100	6.3	9.4	0	
	0.50		31	97	3.2	3.2	0	
	2.0		31	91	9.7	16	3.2	
		Female						
	0		25	89	0	16	0	12
	0.125		30	94	3.3	13	0	20
	0.50		31	97	0	19	3.2	9.7
	2.0		26	81	3.8	15	12	0
		C3H/HeN Male						
	0		43	78	40	2.3	2.3	
	0.125		28	88	61	0	3.6	
	0.50		37	95	70	14	19	
	2.0		48	79	71	6.3	4.2	
		Female						
	0		35	100	11	2.9	0	66
	0.125		29	91	0	0	0	35
	0.50		40	100	18	13	0	94
	2.0		35	79	31	2.9	15	85

Table 9 (contd)

Reference	Dose (Gy)	Strain and sex	Effective no. of mice	Survival rate (%)	Liver tumours (%)	Lymphoma (%)	Adrenal tumours (%)	Ovarian tumours (%)
Ito *et al*. (1992)		$C3B6F_1$ Male						
(contd)	0		34	100	12	0	0	
	2.0		31	97	55	3.2	0	
		$C3B6F_1$ Female						
	0		33	97	0	0	0	6.1
	2.0		27	84	19	3.7	30	0
Takahashi *et al*. (1992)		$B6C3F_1$ Male						
	0		53	96	3.8	Not studied	0	
	0.03		24	100	13		0	
	0.06		24	100	21		0	
	0.125		30	94	37		3.3	
	0.50		30	94	43		0	
	2.0		29	91	62		0	
		Female						
	0		63	95	3.2		0	4.8
	0.125		29	91	3.4		3.4	28
	0.50		30	94	6.7		6.7	80
	2.0		29	91	28		21	62

of soft-tissue tumours only at the highest dose, 0.71 Gy. The total numbers of solid tumours in the lung, liver, gastrointestinal tract, adrenal gland, kidney, soft tissues, mammary gland, urinary bladder, vascular system, bone, Harderian gland, skin and salivary gland were 33, 41, 25, 28, 24, 24, 26, 20 and 27 at the respective doses. There were no differences in survival or tumour incidence between this study at 4 mGy min^{-1} (Di Majo *et al*., 1994) and a previous report (Di Majo *et al*., 1990) in which dose rates of 50 and 250 mGy min^{-1} were used. In a subsequent study, it was shown that male CBA/Cne mice were more susceptible to tumour induction than females (Di Majo *et al*., 1996).

A total of 4689 male and female hybrid $B6CF_1$ (C57BL/6 Bd × BALB/c Bd) mice, 16 weeks of age, were exposed to fission neutrons at doses of 0.06, 0.12, 0.24 or 0.48 Gy in 24 weekly fractions of 0.0025 Gy, 12 fractions of 0.01 Gy every two weeks, six fractions of 0.04 Gy every four weeks or three fractions of 0.16 Gy every eight weeks. A group of 398 male and 396 female controls was available. The animals were observed for life, and tumours were identified histopathologically. The survival and the incidences of most neoplasms increased with dose in the low-dose range (Table 10). Fractionation of the neutron dose did not affect the magnitude of the response at equal total doses (Storer & Fry, 1995).

3.1.2 *Rat*

Most of the studies of the carcinogenicity of neutrons in rats have addressed the effects on the mammary gland (Table 11). The tumour incidence was shown to be influenced by strain and hormonal status (Clifton *et al*., 1975, 1976a,b; Shellabarger *et al*., 1978; Jacrot *et al*., 1979; Shellabarger *et al*., 1982, 1983). The most comprehensive studies are summarized below.

A total of 312 adult female Sprague-Dawley/ANL rats, two to three months of age, were exposed by whole-body irradiation to single doses of 0 (control), 0.05, 0.10–0.12, 0.18–0.22, 0.35, 0.5, 1.5 or 2.5 Gy of fission neutrons (10–15% γ-ray contamination, see Vogel, 1969). The animals were observed for life, and mammary tumours were examined histologically. At the end of the study, the percentages of rats with mammary tumour were 48, 78, 85, 73, 80, 84, 87 and 76% at the different doses, respectively. Of the 126 mammary tumours in 223 rats irradiated with 0.05–2.5 Gy, 66% were benign (67 fibroadenomas, four fibromas, one fibrolipoma, eight adenofibromas and three cystadenomas), and 34% were malignant (13 sarcomas and 30 carcinomas). The RBE in relation to an acute dose of 250-kVp X-rays was 20–60. In a comparison of partial and whole–body exposures to a dose of 0.35 Gy of neutrons, 28 animals received irradiation of one mammary gland at a mean energy of 540 ± 50 keV and 15 animals were exposed to 0.35 Gy of fission neutrons with a mean energy of about 1 MeV. Palpable mammary tumours (mostly fibroadenomas) developed in 75% of those receiving partial irradiation and 80% of those given whole-body exposure (Vogel & Zaldivar, 1972).

Table 10. Survival and incidences of tumours in various organs of BCF_1 mice exposed to single or fractionated doses of fission neutrons

Dose (Gy)	No. of animals	Mean survival (days)	Incidence (%)									
			Lung carci-noma	Reticulum-cell carcinoma	Other lym-phoma and leukaemia	Fibro-sarcoma	Vascular tissue	Liver tumour	Breast carcinoma	Osteo-sarcoma	Ovarian tumour	Other epithelial
Single doses												
Males												
0	398	913	32	17	2.8	29	6.8	8.3	–	–	–	
0.025	396	888	31	22	2.8	32	6.4	9.7	–	–	–	
0.05	393	875	28	23	3.2	36	4.9	11	–	–	–	
0.1	397	870	36	25	2.5	32	5.8	12	–	–	–	
0.2	398	848	39	24	3.5	49	6.8	13	–	–	–	
Females												
0	396	938	13	35	12	6.6	6.1	0.51	9.1	0.76	1.3	
0.025	386	943	12	32	9.3	5.7	6.2	1.6	9.0	0.52	2.6	
0.05	389	926	12	39	14	8.3	8.8	1.5	7.4	0.60	2.4	
0.1	391	895	15	41	12	7.6	9.4	2.9	10	0.94	5.7	
0.2	390	866	21	46	13	5.5	7.5	2.8	9.6	1.7	11	
Fractionated doses												
Males												
0	398	913	32	17	2.8	29	6.8	8.3	–	–	–	1.3
$24 \times 0.0025 = 0.06$	193	875	36	20	3.0	36	2.7	5.9	–	–	–	3.6
$12 \times 0.01 = 0.12$	191	825	41	26	11	47	4.5	9.2	–	–	–	4.5
$4 \times 0.06 = 0.24$	196	825	43	3.1	2.8	49	6.0	11	–	–	–	11
$3 \times 0.16 = 0.48$	199	777	60	43	7.5	67	8.5	15	–	–	–	17
Females												
0	396	938	13	35	12	6.6	6.1	0.51	9.1	0.76	1.3	
$24 \times 0.0025 = 0.06$	194	926	17	42	10	7.1	4.4	–	4.9	0.65	1.9	
$12 \times 0.01 = 0.12$	190	894	13	48	15	11	4.8	2.6	8.4	1.4	3.2	
$4 \times 0.06 = 0.24$	192	841	23	56	20	16	14	12	12	0.93	5.0	
$3 \times 0.16 = 0.48$	194	800	33	68	22	11	3.3	11	12	3.3	11	

From Storer & Fry (1995); –, no tumours

Table 11. Mammary tumours in rats and mice after exposure to neutrons

Species and strain	Dose (Gy)	Mean energy (MeV)	No. of animals	No. of animals with tumours	Incidence of tumours (%)	Reference
Sprague-Dawley/ ANL rat	0	1	89	43	48	Vogel & Zaldivar (1972)
	0.05		27	21	78	
	0.10–0.12		34	29	86	
	0.18–0.22		41	30	73	
	0.35		25	20	80	
	0.50		31	26	84	
	1.50		31	27	87	
	2.50		34	26	76	
Fischer rat	0	Not reported	24	2	8	Clifton *et al.* (1976a)
	0.50		24	17	71	
Sprague-Dawley rat	0	0.43	167	20	12	Shellabarger (1976)
	0.01		182	28	15	
	0.04		89	16	18	
	0.16		68	21	31	
	0.64		45	26	58	
Sprague-Dawley rat	0	14.5	31	2	6.5	Montour *et al*. (1977)
	0.25		30	0	0	
	0.5		30	6	20	
	0.10		25	6	24	
	0.20		25	6	40	
	0.40		25	17	68	
Sprague-Dawley rat	0	1.2	62	2	3	Vogel (1978)
	0.5 + 0.5		40	6	15	
	0.10		38	10	26	
	0.10 + 0.10		29	15	52	
	0.20		29	10	34	
	0.35 + 0.35		35	22	63	
	0.70		37	20	54	
Sprague-Dawley rat	0	14.8	60	1	1.7	Jacrot *et al*. (1979)
	0.6		38	4	11	
Wistar/ Furth rat	0	2.0	18	0	0	Yokoro *et al*. (1980)
	0.48		16	1	6.3	
	0.089		16	0	0	
	0.195		16	0	0	

Table 11 (contd)

Species and strain	Dose (Gy)	Mean energy (MeV)	No. of animals	No. of animals with tumours	Incidence of tumours (%)	Reference
Sprague-Dawley rat	0	0.5	40	Not reported	30	Broerse *et al.* (1987)
	0.02		40		15	
	0.08		40		53	
	0.32		40		63	
	0	15	40		30	
	0.05		40		40	
	0.15		40		65	
	0.50		40		90	
WAG/Rij rat	0	0.5	40		27	
	0.05		40		20	
	0.2		40		33	
	0.8		40		53	
	0	15	40		27	
	0.15		40		35	
	0.50		40		58	
	1.5		40		56	
BN/Bi rat	0	0.5	40		8	
	0.05		40		11	
	0.2		40		19	
	0.8		40		44	
	0	15	40		8	
	0.15		40		22	
	0.5		40		56	
	1.5		40		78	
BALB/c mouse	0	1	263	Not reported	7.9	Ullrich (1983, 1984)
	0.25		140		11	
	0.5		160		17	
	0.10		160		18	
	0.20		167		20	
	0.50		182		25	
	2.00		182		8.4	

Groups of 110 female Sprague-Dawley rats, two months of age, were exposed to single doses of 0.1, 0.2 or 0.7 Gy or to split doses of 0.05 + 0.05, 0.1 + 0.1 and 0.35 + 0.35 Gy at 24-h intervals; 62 rats served as unirradiated controls. The radiation was ^{235}U fission neutrons with a mean energy of 1.2 MeV and a neutron:γ-ray ratio of approximately 7:1. Induction of mammary tumours was examined 11 or 12 months after irradiation [mode of examination not given]. Mammary tumours were reported in 2/62 controls, 10/38 at the single dose of 0.1 Gy and 6/40 given split exposure, in 10/29

at the single dose of 0.2 Gy and 15/29 given split exposure, in 20/37 at the single dose of 0.7 Gy and 22/35 given split exposure. No significant difference was seen in the incidence of mammary tumours with the single and the paired neutron doses (Vogel, 1978).

Groups of 15 and 34 female Long-Evans/Simonsen, 14 and 36 female Sprague-Dawley/Harlan, 15 and 34 female Buffalo/Simonsen, 14 and 36 female Fischer 344/Simonsen and 14 and 36 female Wistar-Lewis/Simonsen rats, two months of age, received whole-body irradiation with a single dose of 0 (control) or 0.5 Gy of fission neutrons (see Vogel, 1969). One year after irradiation, mammary tumours were identified histopathologically. The Long-Evans and Sprague-Dawley strains were the most sensitive, Buffalo and Fischer rats were moderately sensitive, and Wistar-Lewis rats were quite resistant to radiation-induced mammary tumours, the incidences being 56, 56, 29, 26 and 5.5% in exposed rats of the five strains, respectively (Table 12). This result strongly suggested a genetic predisposition in neutron-induced mammary tumorigenesis in rats (Vogel & Turner, 1982).

Groups of 20 (intermediate and high dose) or 40 (control and low dose) female WAG/Rij, BN/BiRij and Sprague-Dawley rats, eight weeks of age, were exposed by whole-body irradiation to single or fractionated doses of monoenergetic neutrons of 0.5, 4 or 15 MeV. In subsequent experiments, the numbers of animals in these groups were increased to 40 and 60, respectively. The animals were observed for life, and tumours were identified by gross and histopathological observation. The three strains developed different types of tumours and showed marked differences in susceptibility for mammary tumorigenesis. The RBE of the 0.5-MeV energy neutrons in relation to acute exposure to 300-kVp X-rays was 15 for the induction of adenocarcinomas and 13 for fibroadenomas in WAG/Rij rats and 7 for the induction of fibroadenomas in Sprague-Dawley rats (Broerse *et al*., 1986, 1987). [The Working Group noted that the numbers of animals in each group were not clearly stated.]

A total of 135 female Sprague-Dawley rats, 35–40 days of age, were exposed to doses of 0.025, 0.05, 0.1, 0.2 or 0.4 Gy of 14.5-MeV energy neutrons produced by a 35-MeV deuteron beam. A group of 31 controls was available. Mammary tumours were identified histopathologically as adenocarcinoma, fibroadenoma (including adenofibroma) and fibrosarcoma. By 11 months after exposure, 2/31 unirradiated rats had developed single fibroadenomas, whereas 42 mammary tumours were reported in 39/135 irradiated rats. The incidence increased with dose, from 0/30 to 6/30, 6/25, 6/25 and 17/25. Six of the rats that died within 11 months after irradiation had mammary tumours. Three rats died with neoplasms at other sites: lymphocytic type lymphosarcoma (0.4 Gy at seven months), osteogenic sarcoma (0.4 Gy at 11 months) and myxosarcoma (0.25 Gy at 11 months). The RBE increased from 5 at 0.4 Gy to 13.8 at 0.25 Gy, when compared with γ-rays (Montour *et al*., 1977). [The Working Group noted that the γ-ray source was not described.]

A total of 551 adult female Sprague-Dawley rats were exposed to 0.43-MeV neutrons at doses of 0 (167 controls), 1, 4, 16 or 64 mGy and the incidences of mammary tumours were examined histologically up to the age of 14 months. At the

Table 12. Mammary tumours in five strains of rat after single whole-body exposure to 0.5 Gy of fission neutrons

Strain	No. of rats with mammary tumours/no. of unirradiated rats	No. of rats with mammary tumours/no. of irradiated rats	All mammary tumours (%)	Fibroadenomas and adeno-fibromas (%)	Adeno-carcinomas (%)	Regressed tumours (%)
Long-Evans/Simonsen	0/15	19/34	56	11	5	0
Sprague-Dawley/Harlan	0/14	20/36	56	8	8	1
Buffalo/Simonsen	1/15	10/34	29	7	3	0
Fischer-344/Simonsen	0/15	9/35	26	6	1	0
Wistar-Lewis/Simonsen	0/14	2/36	5.5	0	1	1

From Vogel & Turner (1982)

end of the study, exposure to 1 mGy was found to have induced a higher incidence (15%) of adenocarcinomas and all other tumours than in the controls (12%). The incidences at the other doses were 18% at 4 mGy, 31% at 16 mGy and 58% at 64 mGy. The first tumours appeared five months after exposure to 1 mGy, three months after 4 mGy, four months after 16 mGy and two months after 64 mGy; in controls, the first tumour appeared at eight months. RBEs of about 100 for the low doses and about 8 for the high doses were reported with reference to an acute dose of 250-kVp X-irradiation (Shellabarger, 1976).

The role of prolactin in the induction of mammary tumours after low-dose whole-body irradiation with fission neutrons was examined in groups of 16–18 female Wistar/Furth rats, seven weeks of age, that were exposed to 0 (control), 0.048, 0.089 or 0.195 Gy of neutrons (mean energy, 2.0 Mev) [γ-ray component not specified]. To promote the development and growth of radiation-induced mammary tumours from dormant initiated cells, prolactin-secreting pituitary tumours (MtT.W95) were grafted subcutaneously 25 days after irradiation. In a further experiment, MtT.W95 were grafted only in tumour-free animals 12 months after irradiation. The rats died naturally or were killed when moribund, and mammary tumours were identified histologically as adenocarcinoma or fibroadenoma. Only 1/48 rats developed mammary tumours after neutron irradiation alone, while 20/48 rats developed mammary tumours when MtT.W95 were grafted 25 days after irradiation. The incidences at each dose were 6/16, 5/15 and 9/17, respectively. When MtT.W95 were grafted in tumour-free animals 12 months after irradiation, the incidences were 4/15, 3/15 and 4/15 at the respective doses (Yokoro *et al*., 1980, 1987).

A total of 767 male and female Sprague-Dawley rats, three months of age, were exposed by whole-body irradiation to fission neutrons at doses of 0.012, 0.02, 0.06, 0.1, 0.3, 0.5 (irradiation period, one day), 1.5, 2.3 (irradiation period, 14 days), 3.9 (irradiation period, 23 days), 5.3 or 8 Gy (irradiation period, 42 days) from a neutron reactor (1.6 MeV; neutron:γ-ray ratio, 3:1) and were observed for the induction of pulmonary neoplasms for life. Tumours were identified histopathologically. The lung tumours included bronchogenic carcinomas, bronchoalveolar carcinomas, lung carcinomas, adenomas and sarcomas. The numbers of animals with lung carcinomas were dose-dependent up to doses of 2.3 Gy, with a reduced mean survival. The numbers of animals with lung carcinoma or adenomas also increased at doses up to 2.3 Gy, but decreased at higher doses. An apparent life-shortening was observed at higher doses (Table 13) (Chmelevsky *et al*., 1984). [The Working Group noted that no data were given on controls.]

A total of 596 male Sprague-Dawley rats, three months of age, were exposed by whole-body irradiation to fission neutrons at 0.016 (mean of the two doses, 0.012 and 0.02), 0.08 (0.06 and 0.10) or 0.40 (0.32 and 0.49) Gy with a mean energy of 1.6 MeV (neutron:γ-ray ratio, 3:1). The duration of exposure was 20 h at 0.016 Gy and 22 h at the other doses. A group of 579 controls was available. The animals were observed for life. Lung carcinomas (bronchogenic and bronchoalveolar) and lung sarcomas were

Table 13. Pulmonary tumours in Sprague-Dawley rats after exposure to fission neutrons

Reference	Dose (Gy)	Irradiation period	No of animals	No. of animals examined	Mean survival (days)	No. of animals with lung carcinomas			No. of animals with lung sarcomas
						Total	Broncho-genic	Broncho-alveolar	
Chmelevsky	0		NR	NR	NR	NR	NR	NR	NR
et al. (1984)	0.012	1 day	150	148	752	4	3		
	0.02	1 day	150	149	741	2	1	1	1
	0.06	1 day	80	77	679	4	1	3	–
	0.1	1 day	78	75	669	6	5	1	–
	0.3	1 day	75	71	584	9	4	5	2
	0.5	1 day	75	72	525	10	7	3	2
	1.5	14 days	40	94	487	14	5	11	3
	2.3	14 days	60	99	450	18	9	10	1
	3.9	23 days	20	20	390	–	–	–	–
	5.3	42 days	19	19	340	4	2	3	1
	8	42 days	20	20	240	2	1		–
Lafuma *et al.*	0		586	579	754	5	4	1	1
(1989)	0.012	20 h	150	149	757	4	3	1	3
	0.02	20 h	150	149	742	2	1	1	2
	0.06	22 h	80	77	679	4	1	3	–
	0.10	22 h	78	75	669	6	5	1	–
	0.32	22 h	75	72	583	9	4	5	2
	0.49	22 h	75	74	522	10	7	3	2

NR, not reported

identified by gross and histological examination. As shown in Table 13, increased incidences of animals with bronchogenic or bronchoalveolar carcinomas were observed. The RBE was 30–40 at the dose of 0.1 Gy and > 50 at the dose of 0.016 Gy in relation to acute ^{60}Co γ-irradiation (Lafuma *et al*., 1989).

A group of 114 female Wistar rats, three to four months of age, were irradiated locally in the region of the liver with 0.2 Gy of neutrons at 14-day intervals for up to two years, for a total of 50 fractions and a total dose of 10 Gy and were observed for life. A group of 114 controls was available. The first liver tumour appeared one year after the beginning of irradiation. At the end of the study, 45 irradiated animals had liver tumours. Of the 83 liver tumours that were classified histologically, 14 were hepatocellular adenomas, 18 were hepatocellular carcinomas, 28 were bile-duct adenomas, nine were bile-duct carcinomas, one was a haemangioma and five were haemangiosarcomas; eight animals had Kupffer-cell sarcomas (Spiethoff *et al*., 1992).

3.1.3 *Rabbit*

A total of 20 male and 18 female adult Dutch rabbits, 7–18 months of age, were irradiated ventro-dorsally with doses of 1.8–5.5 Gy of fission neutrons of about 0.7 MeV mean energy at a dose rate of about 23 Gy h^{-1} with γ-ray contamination of about 2.7 Gy h^{-1}. A control group of 17 rabbits was available. The rabbits were kept for life (six to nine years) and were killed when moribund. Full autopsies were carried out, and the tissues were studied histologically. The mean age at death was significantly lower after the doses of 3.7 Gy and 4.1–5.5 Gy (Student's *t* test). Increased incidences of subcutaneous fibrosarcomas were observed, with 0/17 in controls, 4/15 at 1.8 Gy, 10/16 at 3.7 Gy and 5/7 at 4.1–5.5 Gy. Osteosarcomas were found in 0, 1, 2 and 2 rabbits in the respective groups, and basal-cell tumours of the skin were found in 0, 10, 5 and 1 rabbits, respectively. The RBE for neutrons in relation to acute γ-irradiation was estimated to be 3–3.5 (Hulse, 1980).

3.1.4 *Dog*

A total of 46 male beagle dogs, one year of age, were exposed to fast neutrons with a mean energy of 15 MeV in one of three dose-limiting normal tissues, spinal cord, lung and brain. The radiation was given in four fractions per week for five weeks to the spinal cord, for six weeks to the lung or for seven weeks to the brain. A group of 11 controls was available. The animals were observed for life, and tumours were identified grossly and microscopically. No tumours were reported in the unirradiated controls. Nine neoplasms developed within the irradiated fields in seven dogs receiving fast neutrons, comprising a haemangiosarcoma of the heart (10 Gy to the hemithorax region), an oligodendroglioma and a glioblastoma in the left basal nuclei (13.33 Gy to the brain), an osteosarcoma in the subcutis, an adenocarcinoma of the lung and a haemangiosarcoma of the heart (15 Gy to the hemithorax region), a neuro-

fibroma of the cervical nerve (17.5 Gy to the spinal cord), an osteosarcoma of the vertebrae and a myxofibrosarcoma of the subcutis (26.25 Gy to the spinal cord). The incidence of neoplasia was 15%, and the latent period for radiation-induced cancers varied from 1 to 4.5 years (Bradley *et al.*, 1981).

3.1.5 *Rhesus monkey*

Nine rhesus monkeys (*Macaca mulatta*), three years of age, were exposed by whole-body irradiation to neutrons (^{235}U; energy, 1 MeV) at doses of 2.3, 3.5, 3.8, 4.1 or 4.4 Gy at a rate of 0.08 Gy min^{-1} [γ-ray component unspecified]. A few hours after irradiation, the monkeys were grafted intravenously with $2–4 \times 10^8$ autologous bone-marrow cells (in Hank balanced salt solution) per kg bw. A group of 21 monkeys served as unirradiated controls. Between 4 and 10 years after irradiation, seven animals died with various malignant tumours, including glomus tumours in the pelvis, scrotum and subcutis, sarcomas or osteosarcomas in the humerus, osteosarcomas in the calvaria and papillary cystadenocarcinoma of the kidney and cerebral astrocytoma and glioblastoma. Benign tumours (islet-cell adenoma, subcutis haemangioma and skin fibroma) were also reported. No malignancies were observed in the 21 untreated controls. A RBE of approximately 4 was reported in relation to an acute dose of 300-kVp X-radiation. The latency for death with neoplastic disease after irradiation with fission neutron was 7 years (Broerse *et al.*, 1981, 1991).

3.1.6 *Relative biological effectiveness*

As shown in Table 14, neutrons were generally more carcinogenic than X-rays and γ-rays. Additional studies not described in the text are included in the Table.

3.2 Prenatal exposure

Mouse: Groups of pregnant female BC3F$_1$ [(C57BL/Cne × C3H/HeCne) F$_1$] mice were exposed to 0, 0.09, 0.27, 0.45 or 0.62 Gy of fission neutrons (mean energy, about 0.4 MeV; γ-ray contamination, about 12% of the total dose; minimum and maximum fast neutron dose rates, about 0.049 and 0.248 Gy min^{-1}) on day 17 of gestation and were allowed to deliver their offspring, which were observed for life. Liver tumours were examined histologically. A total of 379 offspring were necropsied. The incidences of liver adenomas and carcinomas were increased to 11, 31, 29 and 52% with the respective neutron doses but decreased to 18% after exposure to the highest dose of 0.62 Gy (Table 15). An RBE of 28 at 0.09 Gy was reported in relation to an acute dose of 250-kVp X-radiation (Di Majo *et al.*, 1990; Covelli *et al.*, 1991a,b).

Table 14. Relative biological effectiveness (RBE) of neutrons for various end-points, in relation to dose and energy

Species	Strain	Effect	Dose (Gy)	Energy (MeV)	RBE	Reference
Mouse	RF/Un	Myeloid leukaemia	0.001	1 and 5	1.8	Upton *et al.* (1970)
		Thymic lymphoma	0.001	1 and 5	3.3	
	RFM	Lung tumour	0.25	NR	25	Ullrich *et al.* (1979)
		Lung tumour	0.10		40	
	BALB/c	Lung adenocarcinoma	0.001	NR	19	Ullrich (1983)
		Mammary tumour	0.001		33	
	CBA/H	Myeloid leukaemia	0.001	NR	13	Mole (1984)
	$B6C3F_1$	Lymphoreticular tumour	0.001	~0.85	2–5	Thomson *et al.* (1985b)
		Lung tumour	0.001		23–24	
		Decreased survival	0.001		15	
	RFM	Myeloid leukaemia	0.001	NR	2.8	Ullrich & Preston (1987)
	$BC3F_1$	Decreased survival	0.01	1.5	12	Covelli *et al.* (1988)
	SAS/4	Lung tumour (male)	< 1	7.5	4.5	Coggle (1988)
		Lung tumour (female)	< 1	7.5	7.4	
	$BC3F_1$	Liver tumour[a]	0.09	0.4	28	Di Majo *et al.* (1990)
		Liver tumour[b]	0.17	0.4	13	
	$B6C3F_1$	Liver tumour (male)	0–2.0	2.13	15	Takahashi *et al.* (1992)
		Liver tumour (female)	0–2.0	2.13	2.5	
	CBA/Cne	Decreased survival (male)	0–0.4	0.4	24	Di Majo *et al.* (1996)
		Decreased survival (female)	0–0.4	0.4	8.6	
		Harderian gland tumour (male)	0–0.4	0.4	20	
		Harderian gland tumour (female)	0–0.4	0.4	9.5	
		Malignant lymphoma (male)	0–0.4	0.4	11	
		Myeloid leukaemia (male)	0–0.4	0.4	2.3	
	C57BL/Cnb	Malignant tumour	0.125–1	3.1	5-8	Maisin *et al.* (1996)

Table 14 (contd)

Species	Strain	Effect	Dose (Gy)	Energy (MeV)	RBE	Reference
Rat	Sprague-Dawley	Mammary tumour	0.001–0.04	0.43	100	Shellabarger (1976)
		Mammary tumour	0.016–0.064	0.43	8	
	Sprague-Dawley	Mammary tumour	0.4	14.5	5	Montour *et al*. (1977)
		Mammary tumour	0.025	14.5	14	
	Sprague-Dawley	Mammary fibroadenoma	0.001	2.43	50	Shellabarger *et al*. (1980)
	ACI	Mammary adenocarcinoma	0.001	2.43	100	Shellabarger *et al*. (1982)
	WAG/Rij	Mammary adenocarcinoma	0.001	0.5	15	Broerse *et al*. (1986)
		Mammary fibroadenoma	0.001	0.5	13	
	Sprague-Dawley	Mammary fibroadenoma	0.001	0.5	7	
	Sprague-Dawley	Lung carcinoma	0.016	1.6–2.1	50	Lafuma *et al*. (1989)
		Lung carcinoma	0.1	1.6–2.1	30–40	
Rabbit	Dutch	All tumours	1.8–5.5	2.5	3–3.5	Hulse (1980)
Rhesus monkey		All tumours	2–4	1	4	Broerse *et al*. (1981)

NR, not reported
[a] Irradiation on day 17 of gestation
[b] Irradiation at three months of age

Table 15. Incidences of liver tumours in male BC3F$_1$ mice exposed *in utero* to a whole-body dose of fission neutrons

Dose (Gy)	No. of mice autopsied	No. of mice with tumours		Incidence (%)
		Adenoma	Carcinoma	
0	230	24	2	11
0.09	49	15	0	31
0.27	42	9	3	29
0.45	25	10	3	52
0.62	33	5	1	18

From Di Majo *et al*. (1990)

3.3 Parental exposure

Mouse: Groups of male C3H mice, seven weeks of age, were exposed by whole-body irradiation to neutrons (^{252}Cf; mean energy, 2.13 MeV) at total doses of 0, 0.5, 1 or 2 Gy and were mated two weeks or three months later with unexposed C57BL females. On day 18 of gestation, some pregnant mice were killed to detect dominant lethal mutations. The incidence of dominant lethal mutations increased in a dose-dependent manner only after postmeiotic exposure, at two weeks. The other pregnant mice were allowed to deliver, and a total of 387 offspring were killed at the age of 14.5 months. Although tumours were found in various organs, only the incidence of liver tumours correlated with exposure to ^{252}Cf radiation, and these tumours were examined histologically. As shown in Table 16, the numbers of liver tumours per male offspring of male mice exposed to 0.50 or 1 Gy ^{252}Cf at either the postmeiotic or the spermatogonial stage were significantly higher than those in unirradiated controls. No increase in the incidence of liver tumours was observed in female offspring. The offspring of male parents irradiated with 2 Gy two weeks before mating did not survive more than two days after birth (Takahashi *et al*., 1992; Watanabe *et al*., 1996).