

RADIATION

VOLUME 100 D
A REVIEW OF HUMAN CARCINOGENS

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 2-9 June 2009

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TO HUMANS

RADIOACTIVE MATERIAL

NEUTRON RADIATION

Neutrons were considered by a previous IARC Working Group in 1999 ([IARC, 2000](#)). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

See Section 1 of the *Monograph* on X-radiation and γ -radiation in this volume.

2. Cancer in Humans

Studies of human exposures to neutron radiation are extremely limited. The major group is the atomic bomb (A-bomb) survivors who were exposed to fission neutrons. Based upon the latest A-bomb dose reconstruction for Hiroshima and Nagasaki, neutron radiation accounted for about at most 1% of the total absorbed radiation dose ([Preston et al., 2004](#)). The neutron component was even less for those in Nagasaki, in which the bomb was plutonium-based in contrast to the uranium weapon used in Hiroshima. Using experimental data, it is assumed that the relative biological effectiveness (RBE) of the A-bomb neutrons is 10 times that of the γ -radiation ([Preston et al., 2004](#)). It has been suggested that this value is too low, and thus the neutron component could account for a greater fraction of the total effective dose in the Hiroshima cohort ([Kellerer & Walsh, 2001](#); [Kellerer et al., 2002, 2006](#); [Sasaki et al., 2006, 2008](#); [Schneider &](#)

[Walsh, 2008](#)). This in turn would reduce the estimated cancer risk of γ -radiation exposures. For example, [Kellerer & Walsh \(2001\)](#) and [Kellerer et al. \(2002\)](#) used values of the RBE in the range of 20–50 for the evaluation of risks for solid cancer from γ -radiation exposure. Although there are city differences, the neutron component of dose is too small to make conclusions about neutron effects and RBE estimates ([Kellerer & Walsh, 2001](#); [Preston et al., 2004](#)).

Nuclear workers are occasionally exposed to neutrons, but their numbers are small, and they typically will also be exposed to higher doses of γ -radiation. Several studies have been carried out on airline crews because of their exposure to neutrons from cosmic rays during high-altitude flights. It is estimated that more than 50% of the effective dose is from high linear-energy-transfer (LET) radiation, most of which is neutron ([Goldhagen, 2000](#)), and the estimated total radiation exposure is in the range of 0.2–9.1 mSv per year, well below occupational limits of 20 mSv per year ([Wilson, 2000](#)). Increases in breast cancer and melanoma have been observed, but not leukaemia. Also, confounding factors include circadian rhythm disruption, which may increase the risk of endocrine tumours, as well as UV exposures and the risk for melanoma. [Sigurdson & Ron \(2004\)](#) summarize well the

studies and issues, and there is not a clear cause and effect relationship between any site-specific cancer risk and employment as a pilot or flight attendant.

Studies of patients treated with neutrons are limited and difficult to evaluate due to the small numbers of survivors and the complex dosimetry often combined with X-rays and chemotherapy agents. Recently, [MacDougall et al. \(2006\)](#) conducted a review of long-term follow-up sites in Scotland, the United Kingdom, of fast-neutron therapy for various cancers among 620 patients. Three cases of sarcomas were reported, which was 111 times the expected in the Scottish population. A study in the United States of America on 484 cancer patients who received neutron therapy reported poor patient survival; only 5% of cases survived 10 years or more ([Sigurdson et al., 2002](#)). Nearly 50% of the study patients were treated for cancer of the uterine cervix, prostate, or head and neck.

3. Cancer in Experimental Animals

3.1 Previous IARC Monograph

Like X- and γ -radiation, neutrons are classified as ionizing radiation. The rationale for most studies of cancer in animals on neutrons have been to quantitatively compare neutron and X- or γ -ray effects as a function of dose to obtain a measure of the RBE for the purpose of weighting risks from neutron exposures compared with those for X- or γ -rays. The following text summarizes the studies reviewed in the previous *IARC Monograph* ([IARC, 2000](#)).

Neutrons have been tested at various doses and dose rates with wide ranges of mean energy from various sources (reactors, ^{252}Cf , ^{235}U) for carcinogenicity in mice, rats, rabbits, dogs, and rhesus monkeys. Fission-spectrum neutrons were used in most of these studies.

In mice, neutrons clearly increased the incidence in:

- myeloid leukaemia and malignant lymphoma including thymic lymphoma ([Upton et al., 1970](#); [Ullrich et al., 1976](#); [Ullrich & Preston, 1987](#); [Covelli et al., 1989](#); [Seyama et al., 1991](#); [Grahm et al., 1992](#); [Ito et al., 1992](#); [Takahashi et al., 1992](#); [Di Majo et al., 1994, 1996](#); [Storer & Fry, 1995](#))
- benign and malignant tumours (e.g. adenocarcinomas) of the lung and the mammary gland ([Ullrich et al., 1976, 1977](#); [Ullrich & Storer, 1979a, b](#); [Ullrich, 1983](#); [Coggle, 1988](#); [Seyama et al., 1991](#); [Grahm et al., 1992](#); [Di Majo et al., 1994, 1996](#); [Storer & Fry, 1995](#))
- benign and malignant tumours of the ovary ([Ullrich et al., 1976, 1977](#); [Ullrich, 1983](#); [Seyama et al., 1991](#); [Grahm et al., 1992](#); [Ito et al., 1992](#); [Takahashi et al., 1992](#); [Storer & Fry, 1995](#); [Di Majo et al., 1996](#))
- benign and malignant tumours of the liver ([Di Majo et al., 1990, 1994, 1996](#); [Seyama et al., 1991](#); [Grahm et al., 1992](#); [Ito et al., 1992](#); [Takahashi et al., 1992](#); [Storer & Fry, 1995](#); [Watanabe et al., 1996](#))
- benign and malignant tumours of the Harderian gland ([Seyama et al., 1991](#); [Grahm et al., 1992](#); [Di Majo et al., 1996](#))
- tumours of the pituitary and adrenal gland ([Seyama et al., 1991](#); [Ito et al., 1992](#); [Takahashi et al., 1992](#)).

Neutrons also induced lipomas ([Seyama et al., 1991](#)), squamous cell carcinomas of the skin ([Di Majo et al., 1994](#)), subcutaneous fibrosarcomas and osteosarcomas ([Storer & Fry, 1995](#)).

In rats, neutrons clearly increased the incidence in malignant mammary tumours ([Vogel & Zaldívar, 1972](#); [Shellabarger, 1976](#); [Montour et al., 1977](#); [Broerse et al., 1986, 1987](#)) and lung carcinomas ([Chmelevsky et al., 1984](#); [Lafuma](#)

et al., 1989). Neutrons also induced benign and malignant liver tumours ([Spiethoff et al., 1992](#)).

In rabbits, neutrons induced subcutaneous fibrosarcomas and basal cell tumours of the skin ([Hulse, 1980](#)).

Neutrons were also tested for carcinogenicity in mice exposed prenatally, and in mice after male parental exposure. In adult animals, the incidences of leukaemia and of ovarian, mammary, lung and liver tumours were increased in a dose-related manner, although the incidence often decreased at high doses. Prenatal and parental exposure of mice resulted in increased incidences of liver tumours in the offspring ([IARC, 2000](#)).

While a γ -ray component was present in the exposure in most studies, it was generally small, and the carcinogenic effects observed could clearly be attributed to the neutrons. Enhancement of tumour incidence was often observed with high doses at a low dose rate. In virtually all studies, neutrons were more effective in inducing tumours than were X-radiation or γ -radiation when compared on the basis of absorbed dose ([IARC, 2000](#)).

Only additional data since the previous *IARC Monograph* will be discussed in the following Section (see also [Table 3.1](#)). The majority of these were reanalyses of historical data.

3.2 Carcinogenicity in adult animals

Studies in adult animals have focused on effects as a function of dose, dose rate or fractionation, and neutron energy.

3.2.1 Mouse

Two studies present reanalyses of previously published data.

The first of these summarized a series of studies conducted over several years comparing neutron and X-radiation effects. Experiments in mice examining carcinogenic effects of single doses of 1.5 MeV neutrons were compared with

250 kVp X-rays, and effects of fractionation were also described. While the sample sizes were small, the studies provide clear evidence for the carcinogenic effects of both fission-spectrum and monoenergetic 1.5 MeV neutrons at doses as low as 100 mGy ([Di Majo et al., 2003](#)).

The second was an analysis of historical data for lung cancer risk derived from a large series of studies conducted at Argonne National Laboratory in 15957 mice with acute and fractionated exposures to γ -rays or fission-spectrum neutrons ([Heidenreich et al., 2006](#)). This analysis reported that at low doses neutrons are approximately 10 times more effective than γ -rays with respect to the induction of lung tumours.

[Watanabe et al. \(2007\)](#) examined tumour induction in mice of both sexes following irradiation at a dose of 500 mGy with monoenergetic neutrons of various energies (0.18, 0.32, 0.6, and 1.0 MeV). No comparisons were made with X- or γ -rays. These studies demonstrated a substantial and significant increase in the incidence of tumours, mainly hepatocellular carcinoma, following neutron irradiation, with no apparent differences among the different neutron energies. Lung, ovary and Harderian gland tumour incidence was also increased.

3.2.2 Rat

[Wolf et al. \(2000\)](#) examined the effectiveness of fission-spectrum neutrons compared to X- and γ -rays for the induction of a variety of tumours with a high degree of lethality in Sprague-Dawley female rats from historical data. Analysis indicated that at doses of 20 mGy, neutrons were approximately 50 times more effective than γ -rays with respect to inducing carcinogenicity.

3.2.3 Rhesus monkey

Two reports on the same cohort of monkeys irradiated with whole-body doses of either X-rays or fission-spectrum neutrons were published by

Table 3.1 Studies in experimental animals exposed to neutrons since [IARC \(2000\)](#)

| Species, strain, sex Duration Reference | Dosing regimen Animals/group at start | Incidence of tumours | Significance |
|--|--|--|--------------|
| Mouse, B6C3F ₁ , CBA (M, F) Duration (NR) Di Majo et al. (2003) | Fission neutrons: M-3 mo-old, received total doses of 0, 25, 50, 100 and 170 mGy delivered in 5 daily fractions or a single dose of 170 mGy F-1 mo-old, received 1.5 Mev neutrons at single doses (0, 5, 10, 20, 40, 80, 160 mGy) Number of animals at start (NR) | 3 mo-old males B6C3F ₁ fractionated Dose-AML, solid tumours (%): 0-0, 16.4 25-0, 20.1 50-0, 17.2 100-0, *26.0 170-2.7, *28.8 Single dose: 170-2.2, *30.4 1 mo-old females B6C3F ₁ Dose-solid tumours, ovarian tumours (%): 0-47.9, 17.2 5-40.5, 23.3 10-44.4, 18.1 20-43.6, 18.1 40-44.6, 19.6 80-58.9, 21.1 160-66.7, 33.3 CBA male Dose-lymphoma, AML, solid tumours (%): 0-4.0, 0, 58.0 10-10.1, 3.8, 77.2 CBA females Dose-lymphoma, solid tumours, ovarian tumours (%): 0-10.3, 41.4, 20.7 10-20.0, 50.0, 10.0 | *P ≤ 0.05 |

Table 3.1 (continued)

| Species, strain, sex Duration Reference | Dosing regimen Animals/group at start | Incidence of tumours | Significance |
|--|--|---|-------------------------------------|
| Mouse, B6CF ₁ (M, F), Duration (NR) Heidenreich et al. (2006) | Acute and fractionated fission neutrons doses, range 10–1500 mGy 15 957 animals | Tumour of the lung: M: RBE for lifetime = 10 For acute neutron vs acute gamma exposures For fractionated neutrons RBE = 4 | |
| Mouse, Crj:B6C3F ₁ (M, F) 13 mo Watanabe et al. (2007) | Single doses of 500 mGy of monoenergetic neutrons at energies of 0.18, 0.32, 0.6 and 1.0 MeV 30/group | Dose–tumours of the liver and lung (%): M– 0–11.0, 0.0 0.18–33.0, 13.0 0.32–31.0, 12.0 0.6–40.0, 7.0 1.0–17.0, 7.0 | $P < 0.05$ irradiated vs control |
| | | Dose–tumours of the ovary, liver, lung, and Harderian gland (%): F– 0.0–0.0, 0.0, 0.0, 0.0 0.18–68.0, 14.0, 4.0, 7.0 0.32–67.0, 4.0, 7.0, 11.0 0.6–54.0, 14.0, 11.0, 25.0 1.0–56.0, 26.0, 4.0, 22.0 | $P < 0.05$ irradiated vs control |
| Rat, Sprague-Dawley Age at start (NS) Lifespan Wolf et al. (2000) | Fission neutrons at dose of 12, 20, 60, 100, 320 mGy 70–150; 795 controls | ERR: 0.0–0 12–1.0 20–2.0 60–6 100–8 320–12 | |

Table 3.1 (continued)

| Species, strain, sex Duration Reference | Dosing regimen Animals/group at start | Incidence of tumours | Significance |
|---|---|---|--------------|
| Rhesus monkey Lifespan Broerse et al. (2000) and Hollander et al. (2003) | Fission neutrons at doses from 2300 to 4400 with a mean of 3400 mGy 9, 21 controls | Malignant tumours: Controls–30% Neutrons–90% Mean absolute age (yr): Controls–28.4 Neutrons–14.9 | |
| Mouse, BC3F ₁ (M, F) Di Majo et al. (2003) | Fission neutrons at a dose of 90 mGy at 17-d post conception | Dose–AML, solid tumours (%): M– 0.0–0, 25.0 90–2.0, 42.9 Dose–solid tumours, ovarian tumours (%): F– 0.0–37.1, 8.6 90–52.4, 14.3 | |

AML, acute myeloid leukaemia; ERR, excess relative risk; F, female; M, male; mo, month or months; NR, not reported; NS, not significant; RBE, relative biological effect; vs, versus

Broerse *et al.* (2000) and by Hollander *et al.* (2003). A total of 20 monkeys were irradiated with X-rays at doses in the range of 2800–8600 mGy, and nine monkeys with fission-spectrum neutrons at doses of 2300–4400 mGy. Controls consisted of 21 age-matched non-irradiated rhesus monkeys. Both types of radiations increased the frequency of a variety of malignant tumours, and decreased their latency compared with non-irradiated controls. In particular, an increase in the incidence of kidney cortical carcinoma was observed (4/9 versus 0/21 controls). Neutrons appeared to be more effective with 90% (8/9) of the neutron-irradiated animals dying with tumours compared to 50% (10/20) following X-ray irradiation and 30% (7/21) in controls.

3.3 Prenatal exposure

3.3.1 Mouse

Effects of irradiation of male and female mice at 17 days post conception with a 90 mGy dose of fission-spectrum neutrons or a 300 mGy dose of X-rays were reported by Di Majo *et al.* (2003). While the numbers of animals were small ($n = 35\text{--}42$), a small but significant increase in total solid tumours as well as ovarian tumours in female mice was observed after the 90 mGy neutron dose.

3.4 Synthesis

Although the number of studies conducted examining the tumorigenic effects of neutrons since 2000 is small, they support and confirm the conclusions of the previous *IARC Monograph*. Neutron radiation has clear carcinogenic effects in a variety of experimental animal studies in mice, rats and monkeys. In addition, neutron irradiation is more effective with respect to its carcinogenic actions than are X- or γ -rays. There is also evidence of an increased incidence of

tumours as a function of dose in several studies in mice and one new study in rats.

4. Other Relevant Data

See Section 4 of the *Monograph* on X-radiation and γ -radiation in this volume.

5. Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of neutron radiation.

There is *sufficient evidence* in experimental animals for the carcinogenicity of neutron radiation.

Neutron radiation is *carcinogenic to humans* (Group 1).

In making the overall evaluation, the Working Group took into consideration the following:

- Every relevant biological effect of X- or γ -radiation that has been examined has been found to be induced by neutrons, including neoplastic cell transformation, mutations *in vitro*, germ-cell mutations *in vivo*, chromosomal aberrations *in vivo* and *in vitro*, and cancer in experimental animals.
- Structural chromosomal aberrations (including rings, dicentrics and acentric fragments) and numerical chromosomal aberrations are induced in the lymphocytes of people exposed to neutrons.

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