3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

The first report of the carcinogenicity of radon was described in 1943 by Rajewsky *et al.*, who reported the occurrence of lung adenomas in mice exposed by inhalation.

(*a*) *Inhalation*

Rat: A group of 12 male SPF Sprague-Dawley rats, weighing 200–250 g, was exposed once to an aerosol of cerium hydroxide dust [chemical and physical characteristics and particle concentration unspecified]; lung retention per animal was estimated to be 0.5–1.0 mg. The animals were subsequently exposed to radon at a concentration of 7.5×10^{-7} Ci/l [27.8×10^{6} Bq/m^3] for 5 h per day on three days per week for a total of 540 h over a period of approximately ten months. Exposure to radon was produced by passing air over a finely-ground ore containing about 25% uranium and circulating it into the inhalation chamber [further details not given]. A second group of 20 rats [presumably of the same strain and weight] was exposed only to 7.5×10^{-7} Ci/l [27.8×10^{6} Bq/m^3] radon for 5 h per day on five days per week for a total of 620 h. Two control groups [number, weight, sex and strain unspecified] were untreated or were exposed to cerium hydroxide only. Animals were killed

when moribund. The authors reported that 'all of the rats still alive in the eleventh month after the beginning of the experiment had pulmonary cancers'. There was no clear statement of tumour incidences in the experimental groups. In the group exposed to cerium hydroxide and radon, 3/12 rats died before the 11th month [no further information given]; thus, presumably, nine developed lung cancers. In the group exposed to radon only, seven animals died of infection before the 11th month, and in three of these that could not be autopsied clear evidence of lung cancer had been seen on previous X-rays; thus, presumably, 16 rats developed lung cancers. All tumours were described as invasive, mixed adeno-squamous carcinomas. Extrapulmonary metastases occurred in one animal only. Most or all of the tumours were believed to be bronchiolar or bronchiolo-alveolar in origin (Perraud *et al.*, 1972).

In a continuation of the study by Perraud *et al.* (1972), groups of 20–200 male SPF Sprague-Dawley rats [age unspecified] were exposed by inhalation to radon-222 to determine dose-effect relationships with radon in different levels of equilibrium with its decay products and the possible interactions of exposures to radon and to stable cerium hydroxide and uranium ore dust. One group was exposed once to an aerosol of stable cerium hydroxide (0.5–1.0 mg deposited per rat lung [physicochemical characteristics unspecified]), followed by exposure to 1.25×10^{-6} Ci/l [46×10^{6} Bq/m^3] radon (in 100% equilibrium with decay products) for 50–600 h over a period of one to ten months. Another group was exposed to 130 mg/m^3 uranium ore dust (15% uranium) for 5-h periods (51 exposures) and to radon on alternate days. Further groups were exposed to cerium hydroxide alone, uranium ore dust alone or to radon alone. Rats were allowed to die spontaneously or were killed when moribund. The tumour incidences and mean survival times are summarized in Table 9. Exposure to radon decay products induced lung tumours at all levels tested, except 21 000 WLM, in which group survival time was reduced from >720 days (controls) to 180 days. The highest tumour incidence (90%) was induced with 9600 WLM. Exposure to cerium hydroxide prior to 6000 WLM radon appeared to shorten latency by three to four months and increased lung tumour frequency (30% after exposure to 7000 WLM radon *versus* 83% after exposure to cerium hydroxide and 6000 WLM radon). Exposure to uranium ore dust did not increase the frequency of radon-induced tumours, and neither cerium hydroxide nor uranium ore dust alone induced tumours. The lung tumours observed were adenomas, adenocarcinomas and squamous-cell carcinomas; bronchiolar and alveolar metaplasia, adenomatous lesions, fibrosis and interstitial pneumonia were also observed. No information was given on tumours at other sites (Chameaud *et al.*, 1974). [The Working Group noted that the level of exposure to radon was very high[1], causing a 90% tumour incidence, which might have prevented the expression of any concomitant effects of uranium ore dust.]

In subsequent studies, dose-response relationships, the effect of radon concentration and the influence of length of exposure were examined. Three-month-old SPF Sprague-Dawley rats [sex unspecified] were exposed and were allowed to die or were killed when

[1]Chameaud *et al.* (1985) revised the estimates of dose in experiments reported previously, updated the data on biological effects, and revised their terminology, replacing the term 'radon-222' by 'radon-222 and radon decay products'.

Table 9. Lung tumour incidence in rats exposed to radon, cerium hydroxide and uranium ore dust[a]

Exposure	Radon decay product equilibrium (%)	Median survival (days)	No. of rats	Rats with lung tumour (%)	No. of benign/ malignant tumours
Control		>720	200	0	–
21 000 WLM – 4 h/day, 75 days	100	180	100	0	–
14 000 WLM – 4 h/day, 50 days	100	265	50	8	2/2
9 000 WLM – 5 h/day, 96 days	20–30	343	20	90	2/16
7 000 WLM – 4 h/day, 25 days	100	485	50	30	6/9
4 500 WLM – 5 h/day, 60 days	20–30	–[b]	40	28	2/9
3 000 WLM – 5 h/day, 40 days	20–30	–[b]	40	13	1/4
500 WLM – 5 h/day, 115 days	1	450	92	10	7/2
Cerium hydroxide		>720	10	0	–
Cerium hydroxide + 6000 WLM – 5 h/day, 108 days	20–30	364	12	83	3.7
Uranium ore dust		498	10	0	–
Uranium ore dust + 9600 WLM – 5 h/day, 96 days	20–30	443	20	85	3/14

[a]From Chameaud *et al.* (1974)

[b]In progress at time of reporting

moribund [further details on experimental procedures not given]. In the first series of experiments, in which radon was filtered continuously to eliminate the action of its decay products, a group of 26 rats received a cumulative exposure of 300–500 WLM (concentration, 150 WL; length of exposure sessions, 5 h). Two rats developed carcinomas, one bronchogenic and one bronchiolar-alveolar. In the second series of experiments, groups of 20–40 rats were exposed to 750, 1500, 3000, 4500 or 9600 WLM (concentration, 2500 WL; length of exposure sessions, 5 h). Lung tumour incidences (bronchogenic and bronchiolar-alveolar carcinomas) were 4/20, 5/20, 17/40, 26/40 and 30/40 in the five exposure groups, respectively. In the third series of experiments, groups of 25 rats were exposed to 2000, 3500, 5500 or 7000 WLM (concentration, 3000 WL; length of exposure sessions, 16 h); and tumour incidences were 7/25, 9/25, 7/25 and 8/25, respectively. Thus, after long exposure sessions, the dose-effect present with shorter exposure is lost, due, according to the authors, to shortening of the lifespan in the latter group. No data on tumours at other sites were given (Chameaud *et al.*, 1976). [The Working Group noted that no data on survival or on frequency of exposure are given.]

Male Sprague-Dawley rats, three months old at the beginning of the experiment, were used to study the effects of low doses of radon on lung cancer incidence. Groups of 500 rats were exposed to a total dose of 20 or 40 WLM by inhalation, and 600 rats were used as controls. Animals were exposed twice weekly for 1 h to 111 000 Bq/m^3 radon for 42 sessions (cumulative exposure, 20 WLM) or for 82 sessions (cumulative exposure, 40 WLM).

Exposure levels were measured with α-track detectors (ISID type) commonly used in French mines. Animals were kept until moribund. Lungs were excised when gross lesions were observed, and those from 80 of the rats exposed to 20 WLM and from 91 of the rats exposed to 40 WLM were examined. The proportions of animals with lung cancer were 0.83, 2.21 and 3.82% in the control, 20-WLM- and 40-WLM-exposed groups, respectively; statistical analysis showed a highly significant trend ($p < 0.006$; one-sided). The distribution of tumour types in the three groups was: one, three and eight squamous-cell carcinomas; three, five and nine adenocarcinomas; and two, three and two bronchiolar-alveolar carcinomas. Statistical analysis of dose effects showed a significant trend for squamous-cell carcinomas ($p < 0.003$) and for adenocarcinomas ($p < 0.02$) but not for bronchiolar-alveolar carcinomas. Statistically significant trends were also found for dose dependance and tumour size ($p < 0.001$) and for pleural invasion ($p < 0.02$). The first tumour at death was discovered at 782, 580 and 498 days in the control, 20-WLM-and 40-WLM-exposed groups, respectively. No information was given on tumours at other sites (Chameaud *et al.*, 1984).

In an article reviewing studies on radon exposure carried out in the same laboratory since 1970, it was noted that rats exposed to radon by inhalation have excess cancer incidence at two extrapulmonary sites — the urinary tract and the upper lip (5/2000 rats exposed to radon and 0/4000 control rats had tumours of the upper lip) (Lafuma, 1978). [The Working Group noted that further details were not given.]

Hamster: Groups of 102 male Syrian golden hamsters, two months old at the start of the experiment, were exposed to room air, 670 WL radon decay products, 790 WL radon decay products with uranium ore dust (22 mg/m^3, count median diameter, 0.19–0.36 μm [no further detail on chemical composition given]) or uranium ore dust (19 mg/m^3). Animals were exposed simultaneously to the various treatments for 6 h per day, on five days per week for life and were killed when moribund (Stuart *et al.*, 1970). No difference in mean body weight or survival was observed between groups [survival unspecified]. After more than one year of exposure, animals exposed to radon decay products with uranium ore dust or to uranium ore dust alone showed evidence of pneumoconiosis, and animals in the latter group had bronchial and bronchiolar hyperplasia, squamous metaplasia and alveolar adenomatosis. During the second year, hamsters exposed to radon decay products with and without uranium ore dust showed 'atypical squamous metaplasia' [numbers and site unspecified]. After 16–17 months of exposure, two hamsters exposed to radon decay products and one hamster exposed to radon decay products plus uranium ore dust showed 'features of squamous carcinoma'. The authors state further that the 'three animals showing these lesions also showed all stages of progression from simple basal cell hyperplasia in bronchioles to malignant tumour' (Wehner *et al.*, 1979). [The Working Group noted the inadequate reporting of the histopathological diagnosis.]

Dog: Male and female beagle dogs, 2–2.5 years old at the beginning of the experiment, were exposed by head-only inhalation to a combination of radon (105 nCi/l [3900 $\times$ 10^3 Bq/m^3]), radon decay products (605 WL) and uranium ore dust (12.9 mg/m^3) plus sham smoking (19 dogs) or to sham smoking only (eight dogs). [Studies on dogs exposed to radon plus cigarette smoke are described in section 3.1(*b*).] The combination of radon decay

products and uranium ore dust had a mass median aerodynamic diameter of 0.6–2.1 μm; the chemical composition was: 75% silicon dioxide, 4% uranium oct-trioxide (U_3O_8), 3% vanadium pentoxide; average concentration, 105 ± 20 nCi/l; average unattached polonium-218, <3%; the levels of unattached lead-214 and bismuth-214 were only fractions of that of polonium-218. The 16-h daily exposure regimes involved 60 min sham smoking, 120 min break, 90 min sham smoking, 4 h radon decay products with uranium ore dust, 120 min break, 60 min sham smoking. Exposures were conducted on five days per week for mixed exposures and on seven days per week for exposure to sham smoking only. All exposures were discontinued 4.5 years after the beginning of the study. Cumulative exposures to radon decay products ranged from 9410 to 15 700 WLM. Survival times after the start of exposure ranged from 34 to 54 months in the treated group and from 52 to 65 months in the controls. Treated animals were killed when moribund; and some control animals were killed at periods corresponding to periods of high mortality in treated animals in order to compare tissues from animals of similar age (one dog after 52 months and three after 65 months). Of the treated dogs, 2/19 developed nasal carcinomas and 7/19 developed lung cancers (three epidermoid carcinomas, three bronchiolo-alveolar carcinomas and one fibrosarcoma). The first of the tumours developed after cumulative exposure to 13 300 WLM radon decay products. No respiratory tract tumour occurred in the eight controls (Cross *et al.*, 1982a).

(*b*) *Administration with cigarette smoke and other compounds*

Experiments in which radon was administered with cerium hydroxide are described on pp. 198–200.

Rat: A group of 100 SPF Sprague-Dawley rats [sex unspecified], three months of age, was exposed by inhalation to a cumulative dose of 3900 WLM radon in equilibrium with its decay products (concentration, 3000 WL; 34 6-h sessions as four night-time sessions per week). One half of the group (50 rats) also received six to ten 10-15-min exposures per day to smoke from a commercial cigarette [composition of cigarette and of smoke and burning rate of cigarettes unspecified] through a cigarette-holder connected to a 500-l box, four times per week for 176 days (total exposure, 352 h). Rats were allowed to die spontaneously or were killed when moribund. A total of 48 rats exposed to radon plus cigarette smoke and 47 exposed to radon only were examined. Seventeen rats exposed to radon only (36%) developed malignant lung tumours compared with 34 rats (71%) exposed to radon and cigarette smoke. Of the tumours, 75% were epidermoid, 20% were adenocarcinomas and the remainder were bronchiolo-alveolar and undifferentiated carcinomas. There was no effect of cigarette smoke on tumour type or latency (Chameaud *et al.*, 1978). [The Working Group noted that no group exposed to cigarette smoke alone was included in this study.]

In an extension of this experiment, using the same exposure conditions, seven groups of 28–50 SPF Sprague-Dawley rats [sex unspecified], three months of age, were exposed to different dose levels of radon in equilibrium with its decay products. Subsequently, four of these groups were exposed to tobacco smoke. In the first experiment, two groups of 50 rats were exposed 34 times to 3000 WL radon for 6 h (cumulative dose, 4000 WLM); one group was subsequently exposed to 10–15-min inhalation sessions with tobacco smoke, four times a week for one year (352 h). In the second experiment, 58 rats were exposed ten times to

3000 WL radon for 3 h (cumulative dose, 500 WLM); 30 of the rats were subsequently exposed to tobacco smoke as in the first experiment. In a third experiment, 58 rats were exposed 17 times to 300 WL radon for 3 h (cumulative dose, 100 WLM), and 30 were subsequently exposed to tobacco smoke as in the first experiment. In a fourth experiment, 45 rats were exposed to tobacco smoke only as in the first experiment. The lung cancer incidence during this lifetime study was: 17/50 treated with 4000 WLM *versus* 34/50 treated with 4000 WLM plus smoke; 2/28 treated with 500 WLM *versus* 8/30 treated with 500 WLM plus smoke; 0/28 treated with 100 WLM *versus* 1/30 treated with 100 WLM plus smoke; and 0/45 animals treated with smoke only. Exposure to tobacco smoke increased tumour size, frequency of pleural involvement, incidence of lymph node metastasis and multiplicity of pulmonary tumours (Chameaud *et al.*, 1982). [The Working Group noted that no data are given on survival or on the origin or histological type of tumours.]

Groups of male SPF Sprague-Dawley rats, five months old, were exposed to a cumulative dose of 6000 WLM radon over a period of ten weeks [further details not given]. Ten weeks after the end of radon exposure, one group of 20 rats received weekly intraperitoneal injections of 25 mg/kg bw benzo-5,6-flavone for 12 weeks. All rats died between 88 and 144 days after the start of benzo-5,6-flavone treatment, and all had lung cancers at multiple sites, mostly epidermoid carcinomas. A group of eight rats received 12 weekly intraperitoneal injections of 25 mg/kg bw benzo-5,6-flavone beginning 65 weeks after the end of radon exposure. Two died 30 and 48 days after the start of benzo-5,6-flavone treatment with no lesion; the remaining six rats all developed pulmonary epidermoid and bronchiolo-alveolar carcinomas within 111 days. A third group (ten rats) was not exposed to radon but received weekly intraperitoneal injections of benzo-5,6-flavone beginning at the same time as the first group, and were killed between 80 and 360 days later. One rat killed at 107 days had an epidermoid lung carcinoma, but the remaining rats had normal lungs. A fourth group (eight rats) was not exposed to radon but received weekly intraperitoneal injections of benzo-5,6-flavone starting at the same time as the second group. Animals died between 20 and 108 days after the beginning of treatment; one had an epidermoid lung carcinoma, but the remaining animals had normal lungs. A last group (40 rats) was exposed to 6000 WLM radon only; 16 rats developed epidermoid and bronchiolo-alveolar lung carcinomas, the first of which appeared at 430 days (Morin *et al.*, 1978). [The Working Group noted that the authors reported that 3-methylcholanthrene appeared to have similar effects; however, the number of animals exposed to radon plus 3-methylcholanthrene is not stated.]

A group of 160 male SPF Sprague-Dawley rats was exposed by inhalation to 3000 WL radon in 100% equilibrium with its decay products for 10 h per day on four days per week for ten weeks (cumulative dose, 6000 WLM). Two weeks after the end of radon exposure, ten groups of ten rats each were given intrapleural injections of 2 mg of various mineral fibres (chrysotile, crocidolite, amosite, glass) or quartz particles. In these combined groups, 66/97 rats (68%) developed pleural and/or pulmonary tumours, compared to 17 pulmonary tumours in 60 rats (28%) exposed to radon only (Bignon *et al.*, 1983). [The Working Group noted that it was difficult to draw any definitive conclusion from this study, because the individual groups were too small, and no control group was exposed only to the various fibres and particles.]

Dog: As reported in section 3.1(*a*), a group of 19 beagle dogs of both sexes, 2–2.5 years old, was exposed by head-only inhalation to a combination of radon (105 nCi/l [3900×10^3 Bq/m^3]), radon decay products (605 WL) and uranium ore dust (12.9 mg/m^3) on five days per week for 4.5 years. A second group of 19 dogs was also exposed to tobacco smoke by inhaling the smoke from ten cigarettes per day for three 60–90-min periods on seven days per week at various intervals between exposure to radon and dust. Lifespan was shortened in both groups in comparison to controls. Eight of 19 dogs exposed to radon and dust alone had nine respiratory tumours, whereas 2/19 dogs in the group that received radon and dust plus cigarette smoke had respiratory tumours (one nasal carcinoma, one bronchiolo-alveolar carcinoma). No respiratory-tract tumour occurred in nine dogs exposed to tobacco smoke alone or in eight controls exposed to sham smoking (Cross *et al.*, 1982a).

3.2 Other relevant data

(*a*) *Experimental systems*

(i) *Deposition, retention and clearance*

Inhaled radon diffuses rapidly in the body, but due to the low solubility of noble gases in body tissues, it is poorly retained in tissues (Hollcroft & Lorenz, 1949). The saturation concentration in tissues is proportional to the radon concentration in the environmental air. For most soft tissues in the guinea-pig, it was in the range of 0.3–0.5 pCi/g wet tissue per pCi/ml air [0.0003–0.0005 Bq/kg per Bq/m^3 air]. In fat, a saturation solubility of about 6 pCi/g per pCi/ml [0.006 Bq/kg per Bq/m^3] has been observed (Pohl & Pohl-Rüling, 1968) (see Table 10).

The deleterious effects of radon result from the deposition of decay products, a fact first recognized in the 1950s (Chamberlain & Dyson, 1956). γ Activity in the respiratory tract of animals that inhaled unfiltered air containing radon and radon decay products was approximately 125 times greater than that in animals inhaling filtered air containing radon alone. In rats, the relative deposition was 1 in the lung, 0.15 in the nasal area and 0.01 in the trachea and large bronchi (Cohn *et al.*, 1953). Unattached radon decay products are deposited rapidly by diffusion (Chamberlain & Dyson, 1956), while the deposition behaviour of the attached fraction is determined by the particle size of the associated aerosol.

The disequilibrium between radon and radon decay product activity in the air of confined spaces depends on the ventilation rate and on the deposition of radon decay products on surfaces. Due to the higher deposition rate of unattached atoms of decay products, enhanced deposition on surfaces leads to a decrease in the relative fraction of unattached polonium-218 atoms (Jonassen, 1984). Direct deposition on the fur of animals may occur (Morken, 1955a). Thus, a retention efficiency as low as 2% was observed in the lungs of rats and mice exposed to radon decay products introduced into an exposure chamber at equilibrium. The use of fans in exposure chambers also resulted in a low equilibrium factor, and most of the decay products were deposited on the walls (Shapiro, 1956). [The Working Group noted that, as reported by Chameaud *et al.* (1985), this effect means that exposure may have been overestimated in some early experiments.]

Table 10. Steady state concentrations in pCi/g wet tissue per pCi/ml air of radon-222 and bismuth-214 in different organs of guinea-pigs after chronic inhalation of radon-222 in radioactive equilibrium with its decay products in air (1 pCi/g per pCi/ml = 0.001 Bq/kg per Bq/m³)[a]

Organ/tissue	Radon-222	Bismuth-214	Equilibrium ratio bismuth-214: lead-214
Lung (average)	–	323	1.7
Stomach and content	0.27	12.8	3.3
Gut and content	0.28	3.9	1.6
Large intestine and content	0.28	1.2	1.1
Blood	0.30	4.5	1.0
Liver	0.30	5.5	1.3
Spleen	0.32	2.2	1.3
Kidney	0.36	21.7	2.3
Urine	–	15.0	3.7
Testis	0.5	1	1
Muscle	0.28	1	1.3
Fat	6	6.1	1

[a]From Pohl and Pohl-Rüling (1968)

Differential distribution in the distal lung, trachea and main bronchi of animals has been measured (Shapiro, 1956; Aurand *et al.*, 1957; Bykhovskii *et al.*, 1972; Duport *et al.*, 1977). Results were strongly dependent on the presence or absence of dust: filtration of air reduced deposition in the distal lung and led to increased deposition in conducting airways. Under chamber conditions, condensation nuclei were formed, and the upper airways were the major deposition site for these very fine particles (0.05 nm) (Duport *et al.*, 1977).

Deposition of nuclei in a model trachea and bronchi was in good agreement with theoretical predictions for laminar flow (Chamberlain & Dyson, 1956). The behaviour of free ions and submicron particles has been studied in excised lung ventilated by air enriched with thoron and its decay products. Turbulence increased the deposition in main-stem and lobar bronchi to two fold that which would have been predicted from laminar flow. Free ions were seen to grow rapidly and their diffusion coefficient was lower than that predicted from models (James, 1977).

In dogs, a half-time of 12 h for clearance of radon decay products after lung deposition was observed using long-lived lead-212 (Bianco *et al.*, 1974). Similar results were observed in ventilated excised lung of pigs (James, 1977) and in tracheotomized rabbits injected intratracheally (Greenhalgh *et al.*, 1977). A study of the location of short-lived α-emitting polonium-214 in the tracheal mucosa of dogs and rabbits indicated that 70% occurred in the mucous layer with an average thickness of up to 10 μm (Kirichenko *et al.*, 1970).

Except for a minor component, which is rapidly cleared to the blood, the predominant mechanism by which radon decay products are cleared is by ciliary action. Removal by

dissolution is slow particularly for bismuth nuclides (Greenhalgh *et al.*, 1977). Clearance half-lives are of the same magnitude as the mucus transit time; in consequence, part of the dose delivered to the airways by lead-214 and bismuth-214 (and equivalents in the thorium series) is due to deposition of particles in the lower part of the bronchial tree. The half-life of polonium-218 is so short that its contribution to the dose in a given region is delivered only to the area in which it is deposited; for the same reason, the contribution of polonium-214 is similar to that of its parent, bismuth-214 (Pohl & Pohl-Rüling, 1968). Lead-210, which is a long-lived nuclide, is not retained in lung tissue and does not contribute significantly to the dose to the lung (Boudene *et al.*, 1977).

The clearance rate of radon from tissues is difficult to measure since the half-lives of its decay products are short; however, distribution in the body of short-lived products can be calculated when equilibrium is achieved under steady-state conditions of exposure (>3 h). Typical distributions are shown in Table 10 which indicates that the highest concentrations of radon decay products are found in the lungs and kidney (Pohl & Pohl-Rüling, 1968). From measurements in rats exposed to high levels of thoron it was shown that, for more long-lived radon decay products (lead-212 and bismuth-212), distribution to the kidney becomes relatively more important (Drew & Eisenbud, 1970).

In experiments to distinguish the relative importance of direct uptake from the lungs and of indirect uptake from the gastrointestinal tract, rats were exposed to radon under steady-state conditions. In animals with an oesophageal ligature, body burdens were marginally lower than in animals without the ligature, indicating that most radon is taken up directly from the lungs (Pohl & Pohl-Rüling, 1968). Uptake from the stomach may be an important factor after ingestion of radon. Radon was exhaled rapidly by mice given radon-rich water, and 80% of the body burden was lost in 20 min; the highest doses were delivered to the gastrointestinal tract and kidneys (Aurand & Schraub, 1954). After intravenous injection to mice of radon in an aqueous solution, the highest dose was delivered to the kidneys (Hollcroft & Lorenz, 1951).

Uptake of lead-210 by the bone contributes to irradiation of the bone marrow. The bone burden of lead-210 in rats and dogs was proportional to the exposure to radon decay products (Palmer *et al.*, 1984).

(ii) *Toxic effects*

An early review of the literature on the biological effects of radon is that of Morken (1955a). Early experiments on the acute toxicity of radon inhalation did not take into account the role of decay products. Radon levels ranging from 0.0005 to 0.02 mCi/l [$18.5–740 \times 10^6$ Bq/m^3] were fatal in rats and mice over periods of three to seven weeks. Cause of death was considered to be due to whole-body irradiation; pulmonary congestion was frequently observed, together with apparent paralysis of the hind-quarters. Autoradiographs revealed high activity on fur, in the lungs and in the adrenal capsule. The lack of information on the state of equilibrium of the decay products used in these early studies (with one exception: Rajewsky *et al.*, 1942) means that no quantitative assessment of dose-effect can be made.

The 30-day LD_{50} of filtered radon in adult mice exposed by inhalation for 1 h was 5.7–8.8 mCi/l [210–320 × 10^9 Bq/m^3] (Morken, 1955b).

In rats, inhalation of radon combined with silica dust resulted in an enhanced silicotic process. Leukopenia was observed only in heavily exposed animals (Kushneva, 1964). The role of radon in the silicotic process was not confirmed in further experiments using similar techniques (Chameaud *et al.*, 1968; Višnjić *et al.*, 1976).

Mice were exposed by inhalation to a mixture of radon and its decay products, polonium-218, lead-214 and bismuth-214—polonium-214, at levels of 0.42, 0.34, 0.20 and 0.1 μCi/l [15.5, 12.5, 7.4 and 3.7 × 10^6 Bq/m^3], respectively, at a constant rate of 1800 WLM per week. Of the available potential energy, 20% was due to unattached polonium-218; most particulate matter was <0.5 μm in diameter. The weekly dose[1] was: lung (lung, trachea, bronchi), 2.8 Gy; gastrointestinal tract, stomach and contents, 0.6 Gy; kidney, 0.18 Gy; and whole body, 0.05 Gy. A 35-week exposure (63 000 WLM) led to a 50% reduction in the normal lifespan; no such effect was observed following 15- and 25-week exposures. Tracheal, bronchial and distal bronchiolar hyperplasia and metaplasia were observed, together with alveolar oedema and focal accumulation of macrophages, some of which contained brown pigment in the lungs. In severly irradiated groups, squamous 'tumourlets' [squamous metaplasia] were also observed in alveoli by the eighth week after exposure (Morken & Scott, 1966; Morken, 1973).

In a series of experiments in which rats were exposed by inhalation to more than 10 000 WLM, increased mortality was reported (Lafuma *et al.*, 1976). In the same series of experiments, a moderate depletion of the lymphoid cell population in the mediastinal lymph nodes was observed following exposure to 3000 WLM (Bonnaud, 1976); following exposure to 6000 WLM, the activity of microsomal enzymes in the lung was increased (Quéval *et al.*, 1979).

In rats exposed by inhalation to radon and radon decay products plus uranium ore dust at 250–1000 WL (cumulative exposures, 320–2560 WLM; unattached fraction, number of nuclei and concentration of dust measured), no significant histological, biochemical or haematological difference was observed between exposed and control animals (Cross *et al.*, 1982b).

In hamsters exposed by inhalation to radon and radon decay products at 690 ± 380 and to radon and radon decay products plus uranium ore dust at 790 ± 330 WL for two to more than 14 months, pulmonary hyperplasia, dysplasia and metaplasia occurred (Cross *et al.*, 1981).

Dogs were exposed by inhalation to 200–10 000 WLM delivered over one to 50 days and were killed after one, two or three years. Measurement of the deposited activity indicated a dose of 0.0017 Gy/WLM to the whole lung, 0.047 Gy/WLM to the trachea and 0.05 Gy/WLM to the main bronchial bifurcation. Foci of subacute inflammation were observed in distal bronchioles and on alveolar walls (Morken, 1973).

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[1]Dose is the quantity of radiation energy absorbed by a medium. Absorbed dose is expressed as Gray (Gy), where 1 Gy = 1 J/kg. Previously, the unit rad was used: 1 rad = 10^{-2} Gy. Dose equivalent is expressed as Sievert (Sv), where 1 Sv = 1 J/kg. Previously, the unit rem was used: 1 rem = 10^{-2} Sv.

Emphysema and inflammatory responses in the lung were observed in dogs exposed to both radon decay products (up to 16 000 WLM) and other airborne pollutants, such as cigarette smoke and uranium ore dust (Cross *et al.*, 1982a).

In rabbits, inhalation of radon was found to modify the electroencephalogram (Ardashnikov & Rait, 1960), as corroborated by the high susceptibility of the cortex in its electrical response to irradiation (Trocherie *et al.*, 1984). Blood corticosteroid levels were reported to be perturbed in rats exposed for 12 days to blood dose-rates of 0.01 and 0.12×10^{-3} Gy/h (Paletta *et al.*, 1976). It was reported in an abstract that the blood cholesterol level was increased in rats 20 h after inhalation of a total dose of 61 μCih/l [2300×10^6 Bqh/m^3]; no effect was observed on blood cells, proteins, glucose or enzyme activity (Tsuchihashi *et al.*, 1982). Continuous inhalation of 5 nCi/l [185×10^3 Bq/m^3] of air by rabbits resulted in atrophy of the sebaceous glands and hyperkeratosis of the lower lip after 30 days; these effects were not observed after exposure to 1 nCi/l [37×10^3 Bq/m^3] (Minta *et al.*, 1975).

Some enzymatic reactions involved in the redox activity of the liver were found to be increased in a dose-dependent manner after ingestion of radon-rich water (0.18–364 μCi/l; 6.7–13 468 $\times 10^6$ Bq/m^3) by rats (Gornak & Ryumshina, 1971). Oral administration to rats after a 50% resection of the gastric fundus of water containing different concentrations of radon modified gastric cytokinetics (Zaporozhchenko, 1973).

(iii) *Effects on reproduction and prenatal toxicity*

No adequate study was available on the effect of radon alone on reproduction or prenatal toxicity. [The Working Group noted that in all the studies reported below, due to the high levels of natural background radiation, the effects of radon and its decay products alone could not be evaluated.]

Male BALB/c mice, three months old, were exposed at a site with high levels of natural radiation and high concentrations of radon in the atmosphere, resulting in exposures of 0.45–0.63 Gy. Controls were exposed in a less radioactive site (0.0013 Gy). After exposure, all animals were mated to nonirradiated three-month-old females over a six-month period. The proportions of sterile pairs were 13/50 (26%) in the control group, 9/51 (17%) in the low-exposure group (0.45 Gy) and 18/38 (47%) in the high-exposure group (0.63 Gy) (Léonard *et al.*, 1985).

In the same study, an unspecified number of female BALB/c mice, three months old, received total doses of 0.15 and 0.0007 Gy and were mated at seven months of age. The average numbers of litters were 1.4 in the treated group and 2.0 in the controls; the average numbers of offspring were 5.0 and 7.7 with 2.9 and 3.9 weaned, respectively (Léonard *et al.*, 1981, 1985).

No change in dental or skeletal measurements, and no effect on fertility or embryonic mortality was observed in black rats (*Rattus rattus* L.) living in an area of high natural radiation in south India (Grüneberg, 1964; Grüneberg *et al.*, 1966).

(iv) *Genetic and related effects*

Adult male *Drosophila melanogaster* were exposed for 24 h to an atmosphere containing radon (obtained from radium chloride) at doses of either 2800 nCi/l [104×10^6

Bq/m^3] (total body dose, 3.26 Gy) or 78 600 nCi/l [2910 × 10^6 Bq/m^3] (total body dose, 510 Gy). Only the higher exposure caused a significant increase in the sex-linked recessive mutation rate (Sperlich *et al.*, 1967) [The Working Group noted that no control experiment was performed, but the spontaneous mutation rate for the X chromosome was used for comparison.]

A dose-related increase in chromosome-type aberrations (dicentrics, rings, terminal and interstitial deletions) was observed in human peripheral blood lymphocytes exposed *in vitro* to α irradiation from short-lived radon decay products at doses of 0.0001–0.003 Gy (Pohl-Rüling *et al.*, 1987).

Male Sprague-Dawley rats were exposed to radon by inhalation at 100–6000 WLM, and samples of bone marrow were prepared at various time intervals from 100 to 750 days. An increase in the frequency of sister chromatid exchanges was observed at all doses. With the highest dose, the increase was observed 100–200 days after the end of exposure, whereas with the lower doses this effect was observed only after a delay of 500–750 days. The authors considered that the increase in sister chromatid exchange frequency was not due to direct radiation damage to the DNA (Poncy *et al.*, 1980).

Five male rabbits were exposed to radon at 10.7 WLM given as 13 separate, 15–20-h exposures over a period of one month. No increase in the frequency of chromosomal aberrations was found in the lymphocytes. In the same study it was reported that an increased frequency of chromosomal aberrations was observed in lymphocytes of rabbits exposed to high levels of natural radioactivity (about 0.7 Gy/year) at a site in France. However, no increase in chromosomal aberrations was found in germ cells from either exposed male mice or their offspring following exposure at the same site (Léonard *et al.*, 1979, 1981). [The Working Group noted that, although the authors suggested that the γ irradiation alone could not have caused this effect, it is not possible to evaluate the effect of the atmospheric radon at the site.]

Increased chromosomal damage was reported in meiotic chromosomes of scorpions (*Tityus bahiensis*) exposed to high levels of natural radiation in Brazil (Takahashi, 1976). [The Working Group noted that the effect of radon and its decay products cannot be evaluated.]

(*b*) *Humans*

(i) *Deposition, retention and clearance*

Deposition of radon decay products is strongly dependent on the characteristics of the aerosol. In mines, the amount of unattached fraction depends on ventilation parameters, and, under typical conditions, most of the attached atoms of decay products are on particles with an activity median aerodynamic diameter of <0.5 μm. The unattached fraction may be larger in indoor air than in mines and the activity median aerodynamic diameter smaller (average, 0.1 μm) (Palmer *et al.*, 1964; United Nations Scientific Committee on the Effects of Atomic Radiation, 1982; National Council on Radiation Protection and Measurements, 1984). The concentrations of radon decay products in indoor air can increase in the presence of cigarette smoke due to an increase in the equilibrium factor. This effect is explained by

reduced deposition of radon decay products on surfaces (Bergman *et al.*, 1986). [The Working Group noted that the dosimetric consequences of this finding are at present uncertain, since the deposition patterns of decay products in the respiratory tract are modified.]

Whole-body counting of workers exposed in a mine atmosphere showed that 70% of the activity was retained in the lung and the rest in the head and neck (Palmer *et al.*, 1964). The deposition and distribution of radon decay products has been studied both by measuring radioactivity in inhaled and exhaled air together with ventilation parameters (George & Breslin, 1967) and by simultaneous recording of the loss of radon decay product energy and of particle concentrations in inhaled and exhaled air combined with external chest counting (Falk, 1984). The fraction of inhaled radon decay products deposited in the respiratory tract was in the range 17–60%, and there was a strong correlation between the number of dust particles deposited and the activity retained. There was no detectable difference for either parameter between mining and residential atmospheres. Breathing *via* the nose increased total deposition by one-third, but the fraction deposited in the tracheobronchial and pulmonary region was decreased by the same amount (Falk, 1984). Tidal volume and flow rate influenced deposition (Holleman *et al.*, 1969). Nasal deposition was found to be extremely high (62%) for unattached decay products and low (2%) for the attached fraction (George & Breslin, 1969).

In common with the other noble gases, radon is distributed in the body in a way that can be fitted by a five-compartment model corresponding to lung, blood, intracellular and extracellular fluids and fat (Harley *et al.*, 1958). The decay in whole-body counts after ingestion of radon in water has been described by simpler models (Andreev, 1966; Suomela & Kahlos, 1972), which are consistent with a retention half-life of 30–50 min.

It is not possible to measure the clearance of short-lived decay products by in-vivo counting of the chest and head, since loss of radioactivity is identical to that of the physical half-lives of the radon-222 series (Palmer *et al.*, 1964; Gotchy & Schiager, 1969). For the longer-lived lead-212, clearance half-times to blood ranging from 6.5 to 12 h have been reported (Booker *et al.*, 1969; Hursh *et al.*, 1969; Hursh & Mercer, 1970).

In miners, levels of lead-210 and polonium-210 in blood and urine are strongly influenced by inhalation of short-lived radon decay products (Bell & Gilliland, 1964; Gotchy & Schiager, 1969); however, Black *et al.* (1968) reported that, three to six months after cessation of mining, the ratio lead urine (measured before death) to lead bone (in autopsy samples) was nearly constant. After occupational exposure, the concentration of long-lived lead-210 in bone may be used as an indicator of cumulative exposure to radon decay products (Black *et al.*, 1968; Wagner *et al.*, 1972; Fry *et al.*, 1983), although some correction has to be made for the clearance of lead-210 due to bone growth. *In vivo*, lead-210 can be measured in the skull at as little as 0.3 nCi (11 Bq), which corresponds to a mean cumulative exposure of 800 WLM (Eisenbud *et al.*, 1969). The contribution of radon gas to the burden of lead-210 in bone is in all cases <10% (Blanchard *et al.*, 1969). In mines, the exact contribution of inhaled dust laden with lead-210 is not known (Blanchard *et al.*, 1969; Gotchy & Schiager, 1969). Lower exposures can be detected by measurements on bone

samples, but detection is limited by an average background burden of 4 Bq/kg bone ash (Fry *et al.*, 1983). For each 1-WLM exposure, 8.4 pCi [0.3 Bq] is deposited in the skeleton (Eisenbud *et al.*, 1969). The mean retention time in other tissues does not reflect long-term exposure (Fry *et al.*, 1983). The lung burden of the long-lived nuclides, lead-210 and polonium-210, in uranium miners is due mainly to decay of short-lived radon decay products (Singh *et al.*, 1985).

(ii) *Toxic effects*

Among 3366 underground uranium miners in the Colorado plateau region, USA, 69 deaths from respiratory disease were observed with 13.9 expected; among 1231 surface workers, 15 were observed with 7.43 expected (Archer *et al.*, 1975). In 192 uranium miners in New Mexico, USA, an impairment of respiratory function was observed which was correlated with time spent underground. Evidence of nodular opacities consistent with silicosis was seen on the chest X-rays of some miners, but it was not possible to determine whether exposure to radon decay products influenced their development (Samet *et al.*, 1984a). A diffuse pneumoconiosis associated with physiological impairment was described in a small number of heavily-exposed uranium miners; however, radon decay products were not considered to be the cause of these abnormalities (Trapp *et al.*, 1970).

In a cohort study of uranium miners in Ontario, Canada, the standardized mortality ratio for all diseases of the respiratory system, including influenza, pneumonia, silicosis and chronic interstitial pneumonia, was 111 based on 53 observed cases; this was not significantly elevated. For the categories 'silicosis' and 'chronic interstitial pneumonia' alone, 11 cases were observed with 2.14 expected ($p < 0.001$) (Muller *et al.*, 1985). [The Working Group noted that the effects observed could not be related to exposure to radon decay products.]

In a prospective study of sputum cytology carried out in 249 Canadian uranium miners, miners who smoked had a higher incidence of abnormal cytology (moderate/marked atypia and cancer cells) than control smokers. For smoking miners, the frequency of abnormal cytology was related to cumulative exposure to radon decay products and to number of years of uranium mining (Band *et al.*, 1980).

A retrospective case-control study was carried out based on 9817 underground miners in the Colorado plateau, USA, for whom sputum cytology had been followed from the 1960s (Saccomanno *et al.*, 1986). The case group (489) was made up of miners with moderate or more severe metaplasia; 992 controls were chosen at random from among miners with negative or mildly atypical cytology. Cases were found to have had a longer mining history, to have been more heavily exposed to radon decay products, to be heavier smokers and to be older.

The studies of Band *et al.* (1980) and Saccomanno *et al.* (1986) both suggest a multiplicative interaction between cigarette smoking and exposure to radon decay products. [The Working Group considered that the degree to which these analyses are informative is limited by the use of cytological abnormalities as the outcome measure.]

(iii) *Effects on reproduction and prenatal toxicity*

Two studies of sex ratio in the offspring of uranium miners (Müller *et al.*, 1967; Waxweiler *et al.*, 1981a) gave contradictory results. No evidence of an effect of uranium mining was reported in a survey of reproductive outcomes in wives of uranium miners and in a control population of wives of potash miners (Wiese & Skipper, 1986).

(iv) *Mutagenicity and chromosomal effects*

Many studies have been devoted to the effect of external γ radiation upon human somatic chromosomes, mostly in peripheral lymphocytes, but relatively few studies have been concerned specifically with the effect of radon and radon decay products. The occurrence of chromosomal aberrations in inhabitants of areas with elevated natural radioactivity has been reviewed by Pohl-Rüling and Fischer (1983). The occurrence of radiation-induced chromosomal aberrations in human somatic cells has been reviewed by the United Nations Scientific Committee on the Effects of Atomic Radiation (1982). [The Working Group noted that lymphocyte cultures harvested at 72 h contain more second- and third-division metaphases than those harvested at 48 h, which generally leads to a loss of cytologically unstable chromosomal aberrations and thus an underestimation of any effect. The Group also noted that, in most of the studies described below, confounding factors such as smoking were not considered.]

Occupational exposures: In a radiological health survey of workers in a plant processing monazite sand (6% thorium oxide, 0.3% U_3O_8) in São Paolo, Brazil, chromosomes in 72-h cultures were studied in lymphocytes from 67 subjects (61 men and six women) selected from three working areas: 'hot' (workers), 'hybrid' (technicians) and 'cold' (administrative personnel). Regression analysis of the cytogenetic variables revealed a slight effect of working area on the rate of dicentrics. Airborne radioactivity was due primarily to thoron decay products, of which lead-212 occurred at 0.002–3.3 pCi/l [0.07–122 Bq/m^3] (Costa-Ribeiro *et al.*, 1975). [The Working Group noted that the radiation exposure of the workers was due mainly to external γ radiation. No attempt was made to estimate the dose to tissues from the different sources.]

Peripheral lymphocyte chromosomes from 80 underground uranium miners and 20 male controls in the Colorado plateau, USA, were studied, taking into account confounding factors such as smoking habits and diagnostic radiation. Five groups with increasing cumulative exposure to radon and radon decay products were selected. Peripheral lymphocytes were cultured for 68–72 h. Pericentric inversions and translocations showed the most consistent pattern of increase with estimated radiation dose. All aberration categories, except dicentrics and rings, demonstrated a significant, uniform increase with dose from <100 to 1740–2890 WLM, but not at >3000 WLM. Significantly more chromosomal aberrations were observed among workers with markedly atypical bronchial cell cytology, suspected carcinoma or carcinoma *in situ* than among miners with regular or mildly atypical cells, as evaluaed by sputum-cell cytology (Brandom *e al.*, 1978).

In a brief summary of a study in China of personnel occupationally exposed to low levels of radiation, an increased frequency of chromosome-type aberrations was reported in lymphocytes (cultured for 54 h) from 55 uranium miners relative to controls (Shu-Yuan *et al.*,

1981). [The Working Group noted that adequate details were not given to evaluate this study and that there was no estimate of the contribution of exposure to radon and radon decay products.]

In a cytogenetic study of 15 Yugoslav coal-fired power plant workers, an increase in chromosomal aberrations in peripheral lymphocytes (cultured for 48 h) was attributed to radiation (Horvat *et al.*, 1980; Bauman & Horvat, 1981). [The Working Group noted that the contribution due to inhalation of radium-226, radon-222 and lead-210 could not be evaluated.]

Exposures in areas with high levels of natural radiation: [The Working Group noted that, in these studies, with the exception of those in Badgastein, Austria, the effect of radon and its decay products alone could not be determined due to the high levels of natural radiation.]

Lymphocyte chromosomes were analysed in 48-h cultures of 180 samples from 122 persons living in Badgastein, Austria, where thermal radon-containing springs discharge 200 mCi [7400 × 10^6 Bq] of radon-222 daily, and where radon also emanates from the ground and buildings. Regression analyses were made relating aberrations to the blood dose of α and γ radiation for: (i) people living and working in the town or surroundings (γ dose 10–140 times higher than α dose); (ii) bath attendants and spa-house personnel (γ dose 10–50 and 0.5–5 times higher than α dose, respectively); and (iii) doctors and thermal gallery train drivers (α dose equal or up to seven times higher than γ dose). An annual blood dose of 1.1–3.4 mGy γ radiation and 0.01–16 mGy α radiation was observed, with dose-effect relationships. Persons continually irradiated showed a steep increase in aberration frequency with dose. Additional occupational doses of α radiation, received intermittently, resulted in a flattening of, and even a decrease in, the dose-related effect (Pohl-Rüling & Fischer, 1979, 1983).

Chromosomes were examined from 202 individuals in Guarapari, Brazil, where the beaches contain 25–30% monazite (a combination of rare-earth phosphates with 6% thorium and 0.3% uranium impurities). External radiation levels range between 0.05 and 0.2 mR[1]/h (peaks up to 2 mR/h) in houses and on some beaches); the average external exposure was 640 mR/year. (According to Pohl-Rüling and Fischer (1983), this would correspond to an annual blood dose of 5.3 mGy/year.) In 72-h lymphocyte cultures, the total number of breaks (measured as one break for a deletion and two breaks for each ring or dicentric) was significantly higher among the exposed population than in controls exposed to normal background radiation. The authors suggested that the high incidence of two-hit type aberrations was caused by the high level of linear energy transfer (LET) radiation in the inhaled airborne radioactivity, and was primarily thoron and its decay products (Barcinski *et al.*, 1975). [The Working Group noted that only about 60 cells from each subject were examined.]

The High Background Radiation Research Group, China (1980) reported the results of two cytogenetic studies of lymphocyte chromosomes from people in two areas with

[1]R = Roentgen

monazite sands and high background radiation and from people in two control regions. The average doses absorbed from external radiation were 1.96 mGy/year in the exposed and 0.72 mGy/year in the control group. The dose resulting from internal radiation was also calculated. The indoor and outdoor concentrations of radon-222 and thoron and their decay products were also measured and the annual doses to the lung calculated. In the first study, 72-h cultures were used and in the second study, 54–56-h cultures. In neither study was the incidence of rings and dicentrics significantly different in the two groups of people.

A subsequent study, performed by the same group and reported in an abstract, showed a significantly higher frequency of chromosomal aberrations in the high-background group than in the controls (Deqing, 1986).

Lymphocyte chromosomes were examined in 48-h cultures from 18 persons living in areas of Finland where household water contains as much as 14.9 mg/l uranium, 9.5 Bq/l radium-226 and 45 000 Bq/l radon-222. Both breaks resulting in dicentric chromosomes and increased numbers of chromosome breaks were significantly more frequent in the exposed group than in nine controls (Stenstrand *et al.*, 1979).

Cytogenetic studies of people living on monazite sand deposits in India and in radon spas in Japan were reported in a review; increases in chromosomal aberration frequency were among the preliminary results (see Pohl-Rüling & Fischer, 1983).

Increased unscheduled DNA synthesis in lymphocytes of persons exposed to radon in the thermal gallery of Badgastein, Austria, was revealed by autoradiography as well as by chromatography after ultraviolet irradiation of the cells *in vitro* when compared with lymphocytes from persons in an area with normal background radioactivity (Tuschl *et al.*, 1980). [The authors interpreted their results as due to a radon-induced increase in DNA repair capacity, but the Working Group considered that further studies were required to support this conclusion.]

3.3 Case reports and epidemiological studies of carcinogenicity to humans

(*a*) *Early case reports*

The association of lung cancer with underground mining in Czechoslovakia was first described in miners working in the Erz mountains in eastern Europe. Metal ores were mined in Schneeberg from the fifteenth century, and in Joachimsthal beginning in the sixteenth century (Hueper, 1966). In the sixteenth century, Agricola (1556) described unusually high mortality from respiratory diseases in miners in the Carpathian mountains. Eleven years later, Aureolus Theophrastus Bombastus von Hohenheim, usually known as Paracelsus, also described respiratory disease in miners in this part of Europe (Hunter, 1969). Härting and Hesse (1879) reported the lung cancer hazard in miners in Schneeberg for the first time. Their report provided clinical and autopsy descriptions of intrathoracic neoplasms in miners, which they classified as lymphosarcoma. Subsequent descriptions of the histopathology established that the malignancy prevalent among miners in the Erz mountains was primary cancer of the lung (Arnstein, 1913; Rostoski *et al.*, 1926). [The Working Group considered that the tumours referred to as lymphosarcomas may have been small-cell

cancers of the lung, which have a histological appearance somewhat similar to lymphosarcoma.] The problem was not recognized in miners in Joachimsthal until 1929, when two cases of lung cancer were reported (Löwy, 1929). Pirchan and Šikl (1932) subsequently described autopsy findings in nine miners with lung cancer, identified from among 19 deaths in Joachimsthal miners during 1929–30.

(*b*) *Uranium mining*

In 1950, the US Public Health Service began an investigation of the miners and millers employed in the uranium mining industry in the Colorado plateau region of the USA (located in Colorado, Utah, New Mexico and Arizona). A prospective cohort study was initiated, and an investigation of mortality is still in progress. The study cohort comprised participants in periodic medical surveys conducted by the US Public Health Service between 1950 and 1960. The criteria for selection included participation in one of these surveys and completion of one month or more of underground mining by 1 January 1964. Two separate cohorts were established; the principal cohort comprised approximately 3400 white miners; results from an additional 780 nonwhite miners, primarily American Indians, were also reported. The concentrations of radon decay products were measured by the US Public Health Service, state agencies and the mining companies; the sources and numbers of the measurements varied by year and geographical region. Between 1951 and 1968, nearly 43 000 measurements of radon decay products were made in the approximately 2500 uranium mines that were worked. Because WL values were not determined directly in all mines annually, estimates were used to complete gaps in the data. WL values were assumed for hard rock mines in which subjects had worked before becoming uranium miners. To calculate cumulative exposure, the annual WL estimates were combined with information on work history collected at annual censuses of active miners and by self-completed questionnaires. [The Working Group considered that these exposure estimates were affected by random misclassification due to the limited number of measurements and the necessity for interpolation and extrapolation.] Measurements after 1960 were taken primarily for control purposes and may have overestimated personal exposures (Lundin *et al.*, 1971). Hornung and Meinhardt (1987) assessed the extent of error associated with each approach used for estimating personal exposure. They calculated that the average coefficient of variation for cumulative WLM is 0.97, that is, 97% of the total WLM for a miner. Information on cigarette smoking was obtained at the survey examinations, at the annual censuses of miners and by mailed questionnaires (Lundin *et al.*, 1971; Whittemore & McMillan, 1983). As described by Whittemore and McMillan (1983), the information was obtained on from one to four occasions between 1950 and 1960 when the surveys were conducted, and on other occasions between 1963 and 1969. [The Working Group noted that assumption of unchanged smoking practices beyond the date at which they were reported is inappropriate because US white males smoked less after the early 1960s.] The occurrence of cancer in the cohort was assessed by statements on death certificate about underlying cause of death. The diagnosis of lung cancer, as ascertained by death certificate, was not further verified. [The Working Group noted that, for lung cancer, the case fatality rate is over 90%.] Mortality in the cohort was determined periodically. Only a few subjects could not be traced, and death certificates were obtained for nearly all deceased subjects. The findings

have been reported for successive follow-up intervals with analyses based on a modified life-table approach (Table 11). The numbers of subjects varied over time as the eligibility and race of the subjects were reclassified. In these analyses, the reference rates for the white males were either those for males in the western states where the mines were located or those for all US white males. For the American Indian miners, the expected rates were those for nonwhites in the states of Arizona and New Mexico. [The Working Group noted that use of rates for all nonwhites, including blacks, overestimates expected values for American Indians in south-western USA.] At all follow-up intervals, lung cancer mortality was increased in the study cohort of white males. Relative risks increased with cumulative WLM (Wagoner *et al.*, 1965; Lundin *et al.*, 1969; Archer *et al.*, 1973a, 1976) (Table 12). Controlling for cigarette smoking using methods based on stratification did not alter the effect of cumulative exposure to radon decay products (Wagoner *et al.*, 1965; Archer *et al.*, 1976). Application of other analytical methods to these data confirmed the findings and extended the description of exposure-response relationships (Lundin *et al.*, 1969, 1971; Hornung & Samuels, 1981; Whittemore & McMillan, 1983; Hornung & Meinhardt, 1987).

Waxweiler *et al.* (1981b) reported cause-specific mortality with follow-up through to 31 December 1977 for the white males. The standardized mortality ratio (SMR) for lung cancer was 482 (185 observed, 38.4 expected). For all sites other than the lung, 79 cancer deaths were observed with 78.8 expected. In no case were SMRs for individual sites significantly elevated.

The south-western American Indian miners in the Colorado plateau region had a low prevalence of cigarette smoking and average consumption by the smokers of only a few cigarettes daily (Archer *et al.*, 1976; Samet *et al.*, 1984b). A statistically significant ($p < 0.01$) excess of lung cancer (11 observed, 2.6 expected on the basis of nonwhite rates [overestimate]) was reported in the 1974 follow-up of the American Indian miners (Archer *et al.*, 1976). Two reports, which included some cases from the cohort reported by Archer *et al.* (1976), also addressed lung cancer risks in American Indians who mined in the Colorado plateau. In a case series of 17 Navajo men from one hospital, all but one had worked as a uranium miner and only two had smoked cigarettes (Gottlieb & Husen, 1982). In a population-based case-control study of lung cancer in Navajo men, 23 of 32 incident cases between 1969 and 1982 had had documented experience in uranium mining, whereas none of 64 matched controls had worked in this industry (Samet *et al.*, 1984b).

Mining of uranium ore in Czechoslovakia began early in this century. A cohort study of lung cancer mortality in Czechoslovak uranium miners has been conducted and the results reported periodically since 1971 (Ševc *et al.*, 1971, 1976; Horáček *et al.*, 1977; Kunz *et al.*, 1978, 1979; Šmid *et al.*, 1983). The initial cohort included 4364 miners who began mining uranium ore between 1948 and 1957 and who had worked underground for at least four years. The more recent reports on this cohort are limited to 2433 miners who began working between 1 January 1948 and 31 December 1952 (Ševc *et al.*, 1971). WL in the mines were calculated from radon gas measurements made from 1948 through to 1959, and from radon decay product measurements made from 1960 through to 1967 (Ševc *et al.*, 1976). The early radon measurements were converted to WL by taking into consideration ventilation and emanation rates from the areas mined. [The Working Group noted that the extent of

Table 11. Results of the study (summarized from principal reports) of white uranium miners in the Colorado plateau, USA

Follow-up cut-off date	No. of subjects	Lung cancer deaths			Comments	Reference
		O	E	O:E		
1959	2666	6	3	2.0	Increase not statistically significant; comparison with white men in the states of the Colorado plateau region	Archer *et al.* (1962)
1957	907	5	1.1	4.6[a]	Cohort members with at least 3 years' experience	Archer *et al.* (1962)
1962	3656	15	4.2	3.6[b]	Includes 1156 workers in surface, open-pit or occasional underground mining through to 1960; comparison with males in the states of the Colorado plateau region	Wagoner *et al.* (1964)
1963	3415	22	5.7	3.9[b]	Response increases with cumulative WLM; comparison with men in the states of the Colorado plateau region	Wagoner *et al.* (1965)
1967	3414	62	10.0	6.2[b]	Excess lung cancer in all exposure categories from 120 to >3720 WLM; comparison with men in the states of the Colorado plateau region	Lundin *et al.* (1969)
1968	3366	70	11.7	6.0[b]	Most comprehensive report; comparison with men in the states of the Colorado plateau region	Lundin *et al.* (1971)
1974	3366	144	29.8	4.8[b]	Response increases with cumulative WLM in all smoking groups; comparison with all US white men	Archer *et al.* (1976)
1977	3362	185	38.4	4.8[c]	WLM not considered in analysis; comparison with all US white men	Waxweiler *et al.* (1981b)

[a] $p < 0.05$

[b] $p < 0.01$

[c] SMR, 482; lower 95% confidence limit, 425

Table 12. Lung cancer deaths by cumulative WLM in white underground miners in the Colorado plateau study[a]

Cumulative WLM	Years after start of underground uranium mining					
	<10			≥10		
	O	E	O:E	O	E	O:E
<120	0	1.16	0.0	1	0.65	1.5
120–359	6	1.56	3.9	6	1.01	5.9
360–839	3	1.30	2.3	11	1.65	6.7
840–1799	2	0.58	3.5	10	1.94	5.2
1800–3719	1	0.16	6.3	20	1.28	15.6
≥3720	2	0.04	50.0	8	0.38	21.1
Total	14	4.80	2.9	56	6.91	8.1

[a]From Lundin *et al.* (1971); follow up, 1950–68

uncertainty resulting from the approach used to estimate exposures cannot readily be quantified.] Personal exposure measurements were maintained after 1968. Information on cigarette smoking was not collected for all subjects, but Ševc *et al.* (1976) reported that the prevalence of cigarette smoking was similar in a group of 700 miners and in the male population of Czechoslovakia. The lung cancer experience of the cohort was determined from registrations of lung cancer in health facilites, records of the industry's hygienic service and notifications of cancer cases from throughout the country. [The Working Group noted that data needed for assessing the completeness of this approach were not reported.] Ševc *et al.* (1976) incorrectly assigned the person-years at risk for each subject to the final cumulative WLM category; this error was corrected in subsequent analyses (Kunz *et al.*, 1978, 1979). The most recent complete report (Kunz *et al.*, 1979) is based on follow-up through to 1975 of miners who first worked between 1 January 1948 and 31 December 1952. The average duration of follow-up was 26 years. Exposure was categorized into five levels of cumulative WLM (≤99, 100–199, 200–399, 400–599 and ≥600) and further classified by three strata of duration of exposure accumulation (Table 13). Excess lung cancer was observed for all levels of cumulative exposure and duration of exposure. For those with the highest exposure, the excess number of cases increased progressively with cumulative exposure. Additionally, the temporal pattern of exposure was classified for each miner as a high followed by a low rate; a constant rate; and a low rate followed by a high rate. A relationship between excess risk and cumulative WLM was evident for miners with a high followed by a low rate of exposure, and for those with a constant rate of exposure, but not for those with an increasing rate of exposure.

Uranium mining began at two locations in the province of Ontario, Canada (Chovil, 1981), in 1955, peaked during the early 1960s, and then rapidly declined (Muller *et al.*, 1983). The epidemiology of lung cancer in Ontario uranium miners has been addressed in three overlapping reports (Ham, 1976; Chovil, 1981; Muller *et al.*, 1983, 1985). A report of the

Table 13. Excess lung cancer per 1000 miners among Czechoslovak uranium miners in relationship to cumulative exposure to radon decay products and years of exposure accumulated (start of exposure, 1948–52; cut-off date for analysis, 31 December 1975)[a]

Cumulative exposure (WLM)	Years of exposure accumulated		
	4.0–7.9	8.0–11.9	⩾2
⩽99	12.6 (−10.3–57.6)[b]	22.7 (−21.4–231.8)	–
100–199	42.5 (21.4–70.4)	53.6 (19.1–106.1)	66.0 (−10.4–293.4)
200–399	43.0 (18.4–77.7)	107.1 (74.5–114.6)	112.1 (67.3–171.6)
400–599	36.4 (−5.1–125.5)	110.4 (64.8–171.5)	155.6 (99.2–229.7)
⩾600	44.1 (−10.9–207.1)	93.0 (26.2–207.2)	189.0 (114.7–289.9)

[a]From Kunz *et al.* (1979)

[b]In parentheses, 95% confidence interval

Canadian Royal Commission on the Health and Safety of Workers in Mines (Ham, 1976) described lung cancer mortality from 1955 through to 1974 for 15 094 persons; all persons had had at least one month of exposure in a uranium mine (see Muller *et al.*, 1981). The 81 lung cancer deaths identified by matching against national vital statistics records significantly exceeded the 45 deaths expected on the basis of rates for the province. In a case-control study conducted within this cohort, cases had had significantly longer duration of mining (43.2 months for cases *versus* 25.6 months for controls) and significantly greater exposure than controls (74.5 WLM for cases *versus* 32.8 WLM for controls). Information on cigarette smoking was not available (Hewitt, 1976).

Chovil (1981) used the records of the Workmen's Compensation Board of Ontario to identify 135 cases of lung cancer in Ontario uranium miners from 1970 onwards. Ascertainment of cases was thought to be incomplete for the period subsequent to 1974. However, crude analyses confirmed the excess of lung cancer in Ontario uranium miners and a relationship between the excess and estimated occupational exposure to radon decay products. Of the 64 cases with smoking histories recorded, none had been nonsmokers. [The Working Group noted that the report was not based on a formally designed study, but on reports of cases to a compensation board. The completeness of coverage of cases in Ontario is not established.]

Muller *et al.* (1981, 1983, 1985) conducted a retrospective province-wide cohort study of mortality from all causes in 15 984 uranium miners in Ontario, Canada, who had received a physical examination between 1 January 1955 and 31 December 1977; had worked at least one month as an underground uranium miner; had not worked at a job involving asbestos exposure; and had not mined uranium in another province as an employee of Eldorado uranium mines. This study is based on the same work histories assembled by the Ontario Workmen's Compensation Board that were used in the study of Ham (1976). Exposure to radon decay products was estimated by different approaches for 1967 and earlier and for

1968 and later: for earlier years, two sets of WLM were developed, one based on the yearly average of the measurement data ('standard' WLM) and the other on a weighted average of the maximum values ('special' WLM). WLM received during other types of underground mining were not considered. After 1967, personal records of exposure to radon daughters were available (Muller *et al.*, 1981). In the initial reports, mortality for the period 1955–77, extended to 1981 in the latest report, was followed up by linkage with national mortality data bases, and cause of death was determined from death certificates. The investigators used the modified life-table technique to compare observed mortality with that expected on the basis of the rates for males in the province of Ontario. Information on cigarette smoking was not obtained. The median year of birth was 1932; the median year of first employment in a mine in Ontario was 1957; and the median duration of mining was 1.5 years. Employment in gold mines in Ontario was also found to increase lung cancer risk; however, the excess lung cancer risk in uranium miners was present for both miners who had and miners who had not mined gold as well as uranium. For those miners with no previous gold mining experience, the mean cumulative WLM was 40, based on the conventionally averaged WL values [calculated by the Working Group]. Overall, the cohort sustained a significant excess of mortality from tracheal, bronchial and lung cancer (119 observed, 65.8 expected; SMR, 181). An exposure-response relationship was evident, regardless of whether the 'standard' or 'special' WLM estimate was used (Table 14). SMRs were also reported for cancers at other sites: no significant elevation was seen for sites other than the trachea, bronchus and lung, but the SMR for stomach cancer was 130 (21 observed, 16.1 expected) and that for bone cancer was 145 (2 observed, 1.38 expected) (Muller *et al.*, 1985).

Uranium was also mined in Canada at mines located in Saskatchewan, and a retrospective cohort study of lung cancer mortality in employees of the Beaverlodge Mine in Saskatchewan has been completed (Howe *et al.*, 1986). The study population included all 10 945 men who were employed in this Eldorado uranium mine between 1948 and 31 December 1980. After exclusions because of missing or incorrect information or because of employment at other company sites, the final cohort comprised 8487 men. Mortality follow-up was accomplished for 1950 through to 1980 by linkage with a nationwide data base. Exposures were estimated for the period 1954–67 from measurements taken for ventilation control purposes; most of the early samples were of radon rather than of radon decay products. The mine staff used these data to estimate individual exposures for the years before 1968. In calculating exposure for previous years, the investigators used the annual median concentration of radon decay products, assumed an equilibrium factor[1] based on the available measurements of radon and its decay products, and assigned exposures on the basis of mine rather than work place averages. [The Working Group noted that such assumptions, often necessary for reconstruction of exposures, may introduce misclassification of exposure. The use of the median rather than the mean may bias exposures downward because of the skewed distribution of measurements of radon decay products in mines.] The 8487 cohort members included 4077 men who had never been employed underground, 3838 who had been employed in underground occupations only, and 572 who

[1]See p. 176

Table 14. Observed and expected deaths from lung cancer by cumulative WLM among Ontario uranium miners with no gold mining experience[a]

Exposure group[b]	Mean exposure (cumulative WLM)[c]	Lung cancer deaths			Person-years at risk
		O	E	O:E	
'Special' WLM					
0.1–10	5	14	9.5	1.47	45 055
10.1–40	22	15	17.4	0.86	62 173
40.1–100	64	12	13.2	0.91	47 154
100.1–170	130	14	6.9	2.03	22 041
170.1–340	235	13	6.4	2.03	18 249
>340	510	14	3.4	4.12	8 124
'Standard' WLM					
0.1–6	3	14	11.7	1.20	51 356
6.1–20	12	13	17.2	0.76	61 823
20.1–40	29	15	11.0	1.36	38 751
40.1–70	53	13	7.0	1.86	23 313
70.1–140	98	12	6.0	2.00	17 345
>140	200	15	4.1	3.66	10 208

[a]From Muller *et al.* (1985)

[b]See text for definition of 'special' and 'standard' WLM

[c]No exposure lag or minium latency period was used in estimating WLM

had been employed in both underground and surface occupations. The underground workers had had an average employment duration of 15 months and a mean age at first employment of 28.8 years. The mean cumulative exposure for the underground workers was 16.6 WLM, whereas that for the surface workers was 2.8 WLM. Mortality in the cohort was compared with expected numbers based on national mortality rates. Information on cigarette smoking was not available. Overall, a significant excess of lung cancer deaths was observed (65 observed, 34.2 expected). In further assessing exposure-response relationships, the investigators excluded the first ten years of follow-up. The SMR for lung cancer increased consistently with exposure (Table 15).

An additional retrospective cohort study of mortality in mines in Canada is in progress, comprising 18 424 men. Nair *et al.* (1985) have examined mortality for employees at four major operations: a pitchblende mine at Port Radium, Saskatchewan, which was later a uranium mine (closed in 1960); a refinery at Port Hope, Ontario; the Beaverlodge uranium mine in northern Saskatchewan; and other sites. The cohorts were established from company records, and follow-up was accomplished by linkage to the national mortality data base for 1950–80. On the basis of follow-up through to 1980, the SMR for cancer of the trachea, bronchus and lung in underground workers at Port Radium was 375 (55 observed, 14.7 expected).

Table 15. Lung cancer deaths by cumulative WLM in 1950–80 (first ten years of follow-up excluded) among Beaverlodge uranium miners in Saskatchewan, Canada[a]

Cumulative WLM	Mean cumulative WLM[b]	Person-years at risk	Lung cancer deaths			Attributable risk[c]
			O	E	O:E (95% confidence interval)	
0–4	0.9	29 818	14	14.46	0.97 (0.53–1.62)	−15 (−288–303)
5–24	11.7	14 815	12	6.48	1.85 (0.96–3.24)	373 (−19–978)
25–49	35.6	5 554	5	2.64	1.89 (0.61–4.42)	425 (−183–1625)
50–99	69.8	3 755	6	2.48	2.42 (0.89–5.26)	937 (−75–2817)
100–149	121.1	1 607	7	1.17	5.99 (2.41–12.35)	3 628 (1024–8248)
150–249	187.4	1 051	6	0.76	7.86 (2.88–17.10)	4 986 (1369–11 705)
⩾250	294.9	342	4	0.28	14.20 (3.87–36.35)	10 888 (2366–29 165)
Total	20.2	56 942	54	28.27	1.91 (1.43–2.49)	452 (216–741)

[a]From Howe *et al.* (1986)

[b]Weighted by person-years at risk

[c][(O−E)/person-years] × 10^6 (with 95% confidence interval)

Tirmarche *et al.* (1984) conducted a retrospective cohort study of men who began working as underground uranium miners during 1947–72 in one of 12 French mines and worked for at least three months. The mortality data were limited to 2442 underground miners followed through to 1983. For 1947–55, WLM values were estimated by an expert committee on the basis of a few radon measurements, ventilation conditions, ore characteristics and working methods. Subsequently, extensive radon measurements were made, averaging about 20–30 measurements per miner and per year during 1957–70 and twice as many from 1971–80. Exposures were estimated as 1–10 WLM monthly for 1947–56, 2.5–4.3 WLM annually during 1956–70 and 3.2–1.6 WLM annually for subsequent years, decreasing regularly from 1971–80. A total of 36 deaths from lung cancer was observed, whereas 18.8 were expected from nationwide data. Smoking histories were not available, and exposure-response relationships were not addressed.

(*c*) *Iron mining*

Exposures to haematite and iron oxide were considered previously (IARC, 1972, 1987). The earlier evaluation (IARC, 1972) was based on case series of lung cancer in iron-ore miners (Faulds & Stewart, 1956; Monlibert & Roubille, 1960; Gurevich, 1967) and on an epidemiological study by Boyd *et al.* (1970). It was suggested that exposure to haematite dust might increase the risk of lung cancer in humans but it was indicated that radioactivity in the air of mines, inhalation of ferric oxide or silica or a combination of these factors might also be of etiological importance. In the later evaluation (IARC, 1987), because of accumulating information on the effects of exposure to radon decay products in underground mining, more emphasis was placed on the role of exposure to radon decay products in haematite mining, especially in view of a recent study of 10 403 Minnesota iron-ore

(haematite) miners that showed no clear excess of lung cancer in the absence of significant exposure to radon decay products (Lawler *et al.*, 1985). That Working Group concluded that underground haematite mining with exposure to radon is carcinogenic to humans (Group 1), and that haematite and ferric oxide could not be classified as to their carcinogenicity to humans (Group 3). (See Preamble, pp. 29–30 for a description of these classifications.)

Snihs (1973) reported the results of a retrospective cohort study of lung cancer mortality in all Swedish nonuranium miners during the period 1961–68. In the approximately 60 mines operating during that time, ferrous and sulphide ores were extracted. Estimates of exposure to radon decay products were based on measurements made during 1969 and 1970 which showed that miners were exposed at >0.3 WL in 22/60 mines and at >1 WL radon decay products in a few mines. An excess of lung cancer was reported in underground miners in comparison with expected numbers calculated from rates in the counties where the mines were located. [The Working Group noted that the methods used for the retrospective cohort study and for estimation of exposure were not adequately described, and the validity of the study could not be assessed.]

Jorgensen (1973, 1984) conducted two investigations of lung cancer mortality among miners in Kiruna, northern Sweden, where iron-ore (mainly haematite) was mined primarily in an open-pit operation until the rapid development of underground mining began in 1950. The presence of radon in the mine was not recognized until 1970 when the first measurements were made. Jorgensen (1973) reported that concentrations of radon decay products ranged from 10 to 30 pCi/l (370–1100 Bq/m^3 EEC_{Rn}) [0.1–0.3 WL] in most locations in the mines, but higher concentrations were measured in some unventilated galleries. The first study was a proportionate mortality study of underground miners employed by the two mining companies in Kiruna (Jorgensen, 1973). All lung cancer deaths in men in the Kiruna district between 1950 and 1970 were identified; and proportionate mortality from lung cancer in underground miners was compared with that in other Kiruna men and in all Swedish men. Thirteen underground workers with lung cancer were identified; 12 had smoked. Regardless of the choice of comparison group, the 13 cases were in excess of expected (4.5 expected in Kiruna men, 4.2 in all Swedish men). Individual exposures were not estimated. In a cohort study of the same two mining companies, 15 lung cancer cases were identified for the period 1971–80 among men who had worked underground; 14 had smoked. The expected numbers were 2.3 for Kiruna men and 4.6 for all Swedish men (Jorgensen, 1984).

In a cohort study of lung cancer in underground miners employed at the Malmberget iron-ore (mainly magnetite) mine in northern Sweden (St Clair Renard, 1974), 14 cases were observed in male miners under 65 years old and still employed within five years of death from 1961 through to 1972, whereas only one was expected on the basis of national rates. A retrospective cohort study of mortality in employees of the Malmberget mine was subsequently conducted by Radford and St Clair Renard (1984). The subjects included 1415 men born in 1880–1919 who were alive in 1930 and had worked underground for more than one calendar year during 1897 through to 1976. Mortality was analysed for 1951–76. Time worked underground was determined from company records, union records and medical

files. The subjects were followed by tracing through parish records, from which the cause of death was determined. The WLM values for individual miners were estimated retrospectively. Radon dissolved in water was assumed to be a major source of radon decay products in the mines, and radon had been measured in water in the mine in 1915. Comparison of measurements made in 1972 and 1975 with the earlier data from 1915 indicated constant radon concentrations in the ground-water. Radon was first measured in mine air in 1968, and both radon and its decay products were measured subsequently. Past concentrations of radon decay products were then estimated on the basis of these measurements and of information on ventilation conditions. Information on cigarette smoking was available for a sample of the miners only. In 1972–73, a questionnaire on smoking habits was administered to active miners and surface workers, and data on 388 active miners and surface workers (about 35% of the active work force at that time) were used; in 1977, 168 pensioners responded to a questionnaire. By the end of follow-up, 532 of the 1415 miners had died. The average year first employed underground was 1932 and the average duration of underground exposure was 19.5 years. The miners had an average exposure of 4.8 WLM/year, and total cumulative exposures ranged from 2 to 300 WLM, with an average of 93.7 WLM. In comparison with expected rates based on the Swedish general population, excess mortality was found for lung cancer (50 observed, 12.8 expected) and for stomach cancer (28 observed, 15.1 expected). For all other cancers, the SMR was 102 (61 observed, 59.7 expected). Lung cancer risk increased with cumulative exposure to radon decay products (Table 16). Agents other than radon decay products that might have been associated with the increased lung cancer risk were addressed: neither tuberculosis nor silicosis could be linked to the lung cancer excess; and diesel engines had not been introduced in the mines until the 1960s. Furthermore, an excess of lung cancer was observed in both smokers (32 observed, 11.0 expected; 90% confidence interval [CI], 2.1–3.9) and nonsmokers (18 observed, 1.8 expected; 90% CI, 6.5–14.8).

Table 16. Lung cancer deaths in iron-ore miners in Malmberget, Sweden, by cumulative WLM[a]

Exposure (WLM)	O	E[b]	O:E
0–49	8	3.4	2.4
50–99	14	3.6	3.9
100–149	4	2.5	1.6
150–199	18	2.4	7.4
⩾200	6	1.0	6.3

[a]From Radford and St Clair Renard (1984)

[b]Based on national rates for Sweden, corrected for the effect of smoking

Damber and Larsson (1982) conducted a case-control study of lung cancer in the three most northern counties of Sweden, an area that includes the municipalities of Kiruna and

Gällivare (encompassing Malmberget), where iron ore mines are located, and covering the same mines as in the previous studies. The case series comprised the 604 dead cases with lung carcinoma diagnosed during the period 1972–77; two matched-control series included 604 dead men and 467 living men. Information on employment history and cigarette smoking was obtained by interview with next-of-kin for the dead cases and controls and directly from the living controls. Years of employment in underground mines were used as the measure of exposure; WLM were not estimated. The unadjusted relative risk for underground exposure of at least one year was 2.5 (95% CI, 1.2–5.2). The average interval from first employment underground to appearance of cancer was 34.8 years. Damber and Larsson (1985) subsequently extended the period of the study within the municipalities of Kiruna and Gällivare to cover 1972–82. The unadjusted relative risk for lung cancer for underground mining was again elevated (4.6; based on 69 cases) and increased with duration of employment. The median interval between employment as an underground miner and cancer diagnosis was 39.5 years.

Edling (1982) used a case-control approach in conducting a study of lung cancer deaths from 1955 through to 1977 in an iron-ore mine in southern central Sweden. The study comprised 47 cases and 897 controls. Occupational history was obtained from the mining company and smoking history by interview with next-of-kin. The age-adjusted odds ratio was 16.2 for underground mining ($p < 0.0001$).

Faulds and Stewart (1956) reported an unexpectedly high frequency (9.4%) of lung carcinoma in iron-ore (haematite) miners in West Cumberland, UK, on the basis of autopsy information for 1932–53. Mortality in the same mining district during 1948–67 was subsequently examined using a proportionate mortality approach (Boyd *et al.*, 1970); lung cancer mortality was increased by about 75% in underground iron-ore miners (36 observed, 20.6 expected from local rates). Levels of radon decay products had been found to be elevated (0.3–3.2 WL) in three West Cumberland mines (Duggan *et al.*, 1970); however, exposures were not estimated for individual miners. Kinlen (1984) examined the mortality of these iron-ore miners for 1948–67 and found 50 lung cancer deaths, whereas 31.4 were expected on the basis of mortality rates for rural areas.

Several case series have suggested an excess occurrence of lung cancer in miners working in iron-ore mines in Lorraine, France (Roussel *et al.*, 1964; Anthoine *et al.*, 1979). In 1975, a prospective cohort of 1173 workers was selected randomly from among the 5300 workers actively employed in Lorraine iron mines (Pham *et al.*, 1983). The cohort comprised 185 surface and 988 underground workers. Mortality in the cohort was determined through to 1980 using records from the mines' medical services, from hospitals and from clinicians. An SMR of 350 for lung cancer was found (13 observed, 3.7 expected on the basis of national rates). All of the men with lung cancer had worked underground for an average of 25.2 years, and all were smokers. Individual exposures to radon decay products were not estimated, but the authors reported exposures to radon and its decay products of 0.03 WL at work sites and levels as high as 0.4 WL in abandoned and poorly ventilated places.

Leira *et al.* (1986) conducted a retrospective cohort study of Norwegian miners employed at an underground mine producing magnetite, pyrite and copper sulphide. At this mine, Fosdalen, mean exposures to radon decay products at different sites varied from 0.10

to 0.15 WL. A comparison mine, Løkken, was chosen because similar ore was mined there, but exposures to radon decay products were ≤0.02 WL. The study cohort included 332 male underground miners from Fosdalen and 190 from Løkken. All had worked for at least three months underground, had been employed from 1940 through to 1959 for more than 36 months and were alive on 1 January 1953. Follow-up was carried out from 1953–80 for mortality and cancer incidence. Expected numbers of lung cancer were based on nationwide and county rates. Four lung cancer cases were observed at Løkken (1.8 expected on the basis of national rates) and three at Fosdalen (2.8 expected on the basis of national rates). For Fosdalen, the expected number dropped to 1.8 when county rates were used.

(*d*) *Other mining*

Open-pit mining of fluorspar (calcium fluoride) began in St Lawrence, Newfoundland, Canada, in 1933, but was replaced three years later by conventional underground mining (de Villiers & Windish, 1964; Morrison *et al.*, 1981). During the 1950s, an apparent excess of lung cancer was noted among the fluorspar miners, and environmental studies and an epidemiological investigation were implemented. The initial environmental survey showed high levels of radon, even though the ore itself is not radioactive; the radon source was found to be water seeping into the mines. Between 1933 and 1961, 26 lung cancer deaths were identified among fluorspar miners. By proportionate mortality analysis, lung cancer mortality during 1952–60 was found to be increased by 29 fold (21 observed, 0.73 expected) (de Villiers & Windish, 1964). More recent reports on these miners have included assessment of exposure-response relationships (Morrison *et al.*, 1981, 1985). Mortality of 2120 miners, millers and surface workers employed from 1933 to 1978 was examined through to 1981. Exposures were estimated on the basis of occupational histories that included type and place of work and hours of work by year up to 1960; from 1960 onwards, exposures to radon decay products were available by calendar year. For the years before 1960, hours of work were converted to working months and used to calculate WLM. WL values were estimated retrospectively from measurements made in only one mine in late 1959 and early 1960. (Before 1960, the mines were ventilated primarily by natural draft, occasionally aided by small blowers, and the ventilation varied greatly by mine, as did the amount of water seepage.) Radiation measurements were made more frequently during 1960–68, and daily exposures were estimated for each miner after 1968. Analysis was based on a standard modified life-table approach using age-specific rates among the surface workers for comparison. [The Working Group noted that only seven lung cancer deaths occurred among the surface workers, and the comparison mortality rates cannot be considered stable.] Analysis based on follow-up through to 1981 showed an exposure-response relationship between lung cancer mortality and cumulative WLM (Table 17).

Wagoner *et al.* (1963) conducted a retrospective cohort study of mortality until 1959 among long-term underground metal [unspecified] miners in the USA. Eligibility for the cohort was based on at least 15 years' experience before 31 December 1948. A total of 1759 men met these criteria. Using conventional cohort analysis and comparison rates from the white male populations of the same western states, a three-fold excess of lung cancer deaths (47 observed, 16.1 expected) was seen. The miners had been exposed to radon and radon

Table 17. Lung cancer deaths in fluorspar miners in Newfoundland, Canada, 1933–81[a]

Cumulative exposure (WLM)	O	E[b]	O:E
0	7	7	1.0
1–9	3	2.0	1.5
10–239	13	7.2	1.8
240–599	10	3.9	2.6
600–1079	6	1.7	3.5
1080–2039	25	1.5	16.2
⩾2040	40	1.0	39.2

[a]From Morrison *et al.* (1985)

[b]Excludes person-years from the first ten years after the start of mining

decay products, and measured concentrations of radon in the mines in 1958 were 10–80 pCi/l [370–2960 Bq/m^3]. Neither individual exposure estimates nor information on smoking were available.

High levels of radon and its decay products have been measured in tin mines in Cornwall, UK. Fox *et al.* (1981) conducted a retrospective cohort study of mortality among 1333 men employed in two tin mines in Cornwall during 1939. In comparison with mortality rates for England and Wales, lung cancer mortality was increased in the underground miners (28 deaths observed, 13.2 expected; SMR, 211) but not in surface workers (SMR, 74) or in those workers whose occupation was not classifiable (SMR, 94). WLM were not estimated, but the authors reported governmental estimates of 25 and 15 WLM annually for the two mines, respectively.

Tin has been mined in the Yunnan region of China for centuries (Shiquan *et al.*, 1984). Wang *et al.* (1984) identified a cohort of 12 243 underground miners and calculated lung cancer incidence and mortality in this group for the period 1975–81. While the age distribution of the cohort is not given, it has been reported that many persons in that region began underground mine work between the ages of eight and 14 (Shiquan *et al.*, 1984). This practice was phased out around 1949. WL were calculated from detailed individual work histories and systematic measurements of radon decay products at underground work sites during 1972–80. Only natural ventilation was employed in the mines from 1953–72, so exposures were assumed to have been constant during this interval. Prior to 1953, some of the mines were smaller and wet mining methods were not used; thus, 'proportionate' adjustments were made. Another undescribed adjustment was made for exposures prior to 1949, when more primitive mining methods, including back-carrying of ore through narrow tunnels, were employed. During the follow-up period, the average annual incidence of lung cancer was 515.4 per 100 000 (499 observed) among underground miners and 41.3 per 100 000 (59 observed) among surface workers. Analyses by estimated cumulative exposure

showed increasing SMR with cumulative exposure. Shiquan *et al.* (1984) described an excess of lung cancer cases ascertained during 1954–78 among workers at three tin mines in Yunnan.

A cohort of 112 Swedish zinc-silver-lead miners aged less than 67 years from two adjacent mines had seven lung cancers in the period 1956–70, with 0.53 expected. There were seven additional cases in retired miners, but the expected numbers could not be calculated (Axelson & Rehn, 1971). Axelson and Sundell (1978) conducted a case-control study of lung cancer in Hammar parish, Sweden, the site of the two zinc-lead mines. For each of 29 cases of lung cancer death identified for the period 1956 through to 1976, three deceased controls were selected. Employment in underground mining was established by reviewing company records, and the smoking habits of the miners were established by review of records and interview of two former foremen. Twenty-one of the 29 cases had been exposed to underground mining compared with 19 of 174 controls. The age-adjusted relative risk was 16.4. Exposure to radon decay products was not measured for individual miners, but was estimated to have been at about 1 WL.

Solli *et al.* (1985) followed a cohort of employees at a Norwegian niobium mining company that operated from 1951–65. The 318 male subjects included only 77 miners. The ore contained uranium-238 (0.3–2 ppm [mg/kg]) and thorium-232 (50–300 ppm [mg/kg]). Exposure to both radon and thoron decay products in 1959 was calculated, on the basis of measurements of α activity, to have been as high as 300 WLM. In 1959, the mean exposure to radon decay products was 1.0 WL and that to thoron decay products 0.2 WL. Mortality and incidence were ascertained from 1953 through to 1981 and compared with national rates. In miners, nine lung cancer cases were observed whereas 0.81 were expected. Among all employees, a steep exposure-response curve was found between lung cancer risk and cumulative WLM.

(*e*) *Nonoccupational exposures*

The measurement of relatively high indoor levels of radon and radon decay products has prompted a number of studies of lung cancer among individuals living in different types of houses, implying varying degrees of exposure. A number of case-control studies have been undertaken in relation to defined indicators or measurements of indoor radon.

Axelson *et al.* (1979) studied lung cancer in a totally rural Swedish population of approximately 11 300 inhabitants aged 40 years and over in relation to the building materials and basement construction in their houses. These factors are known to influence indoor radon levels, which are generally lowest in wooden houses and highest in stone houses, with intermediate levels in brick houses; the existence of a basement is thought to increase indoor radon. Thirty-seven lung cancer cases and 178 noncancer referents, all deceased, were obtained for the study during the period 1965–77. The house of last residence was put into one of three categories: wooden houses without a basement (category 0), stone houses with a basement (category 2) and all other houses (category 1). A significant exposure-response relationship was obtained; combination of categories 1 and 2, in comparison with category 0, gave an odds ratio of 1.8 (90% CI, 0.99–3.2). Residence in a wooden house was estimated to have resulted in a lifetime exposure of 1.9 WLM, *versus*

3.9 WLM for people living in houses of the combined categories 1 and 2 (Axelson & Edling, 1980). Exposure at work and out of doors was estimated to be 0.5 WLM per lifetime for all categories.

A similar study of lung cancer in relation to indoor radon levels was carried out on the Baltic island of Oeland, which has a narrow alum-shale strip emanating radon along which a large part of the population lives; the rest of the island consists of limestone and has low radioactivity. An estimated average number of 5456 men and women aged 40 years and above had lived on the island and in the same house for 30 years or more between 1960–78, constituting the base population for the cases and controls. Exposure estimates were based on type of house and potential leakage of radon from the ground; in the final analysis (Edling *et al.*, 1984), measurements of radon decay product concentrations, by cellulose nitrate film, were also taken into account, as well as smoking. Twenty-three deaths from lung cancer and 202 dead, noncancer controls fulfilled the criteria for involvement in this final analysis. Exposure was divided into three categories — 0, 1 and 2, as described above in the study of Axelson *et al.* (1979); the Mantel-Haenzel odds ratios were 1.0 (category 0), 1.2 (90% CI, 0.5–3.1; category 1) and 4.3 (90% CI, 1.7–10.6; category 2). There was also a significant trend over the exposure categories. Measured mean radon decay product concentrations were 42, 57 and 170 Bq/m^3 EEC_{Rn} in the three categories, respectively. Data on smoking were available for all but one case and 24 controls, and an analysis involving only subjects with known smoking habits gave essentially the same results (Edling *et al.*, 1986).

Pershagen *et al.* (1984) estimated indoor radon exposure in Sweden on the basis of type of house for two sets of 30 pairs of dead lung cancer cases and controls matched by year of birth and smoking habits. One of these sets of pairs — 15 smoking and 15 nonsmoking —was obtained from the cancer registry in northern Sweden and the other from the national twin registry. Smoking cases from northern Sweden were found to have had significantly higher estimated exposure to radon than smoking controls (30.1 *versus* 24.5 Bq/m^3 × months; $p < 0.02$; one-tailed), whereas no clear difference was seen for the nonsmoking cases and their controls or for any of these categories among the twins.

Damber and Larsson (1986) studied 604 dead male lung cancer patients and two sets of male controls [of which the previous study (Pershagen *et al.*, 1984) included a subset, as did the study of miners (Damber & Larsson, 1985)], one living and one dead, matched for year of birth and municipality and, when appropriate, for year of death, and with regard to the type of house in which they had lived since the age of 20 for life. For those born prior to 1900, only dead controls were drawn. The cases had been reported to the Swedish Cancer Registry for the three most northern counties in the period 1972–77. Detailed information on quantity and duration of smoking was obtained, and potential exposure to radon, on the basis of building material of walls only, was estimated. Only weak associations of risk with living in nonwooden houses were obtained. When individuals with known risk occupations were excluded, the risk increased. Hence, the adjusted odds ratios were 1.5 (95% CI, 0.9–2.3) and 2.0 (1.0–4.0) for 1–20 and >20 years in nonwooden houses, respectively, for persons with no risk occupation. No estimation was made of exposure to radon and its decay products.

Svensson *et al.* (1987) reported a study from 1972–80 of 292 women with oat-cell or other anaplastic types of lung carcinoma and 584 age-matched population controls. All persons had lived in Stockholm for at least 30 years, and controls were alive at the time of diagnosis of their corresponding cases. Two exposure categories were used: 'radon risk' and 'no radon risk'. Radon measurements were taken in 10% of the houses in which the subjects had lived. In order to be classified as 'exposed', a subject had to have lived either in a detached house or on the bottom floor of a multi-family house on ground emitting significant amounts of radon. An odds ratio of 2.2 (95% CI, 1.2–4.0) was obtained. Data derived from a national survey by community indicated that the smoking frequency in areas with 'radon-positive addresses' was similar to that for the population of Stockholm as a whole. Mean exposure levels for cases considered to have been exposed were 55 Bq/m^3 EEC_{Rn} and their average residency, 15.8 years. Cases considered not to have been exposed and exposed and nonexposed controls had mean exposure levels of 24.8–38.7 Bq/m^3 EEC_{Rn} and residencies of 16.4–18.2 years.

A case-control study was carried out in Port Hope, Ontario, Canada, to evaluate the possible effect of exposure to radon from waste material from ore processing and from the recovery of radium. Cases were considered to be any individuals who had developed or died of lung cancer between 1969 and 1979. Twenty-seven cases and 49 controls met the inclusion criteria, one of which was to have lived for at least seven years in the town and not to have had occupational exposure to radioactive materials. The controls were either alive with or without other cancers or dead from other cancers. Exposure was estimated on a cumulative basis with regard to the houses the subjects had lived in, but the average annual background exposure of 0.23 WLM was subtracted so that only excess exposure was considered. Contrasting 'zero WLM' with 'non-zero WLM' and controlling for smoking, a marginally significant association (odds ratio, 2.4) was found between exposure and lung cancer ($p = 0.057$; one-sided). When log-transformed WLM estimates were used as a continuous variable, a significant ($p = 0.014$) positive association was observed between exposure and lung cancer, with estimated odds ratios of 1.0 (reference), 1.1 (1 WLM), 6.4 (5 WLM) and 11.9 (10 WLM). The authors concluded, however, that the analyses had not provided conclusive results that linked an increased risk of lung cancer to elevated domestic α radiation levels (Lees *et al.*, 1987).

A number of correlation studies have been carried out addressing the relationship of environmental radiation, including radon, and cancer, in which individual exposure is not documented (Fleischer, 1981; Bean *et al.*, 1982; Edling *et al.*, 1982; Hess *et al.*, 1983; Simpson & Comstock, 1983; Dousset & Jammet, 1985; Forastiere *et al.*, 1985; Hofmann *et al.*, 1985; Wilkinson, 1985).

(*f*) *Quantitative considerations of lung cancer risks*

Several task groups and individuals (United Nations Scientific Committee on the Effects of Atomic Radiation, 1977; Committee on the Biological Effects of Ionizing Radiations, 1980; International Commission on Radiological Protection, 1981; National Council on Radiation Protection and Measurements, 1984; Thomas *et al.*, 1985; International Commission on Radiological Protection, 1987) have attempted to reconcile the results of

epidemiological studies of miners exposed to radon decay products in order to quantify the risk associated with such exposure and to elucidate the role of smoking and temporal characteristics of exposure in radiation-induced lung carcinogenesis.

Tables 18 and 19 summarize, respectively, the main characteristics of the available epidemiological studies on occupational exposures to radon and its decay products, and the results of risk estimations performed by the original authors as well as by subsequent investigators and task forces.

Table 18. Summary of principal cohort studies of radon-exposed miners

Location	Substance mined	Years of follow-up	Mean cumulative exposure (WLM)	Lung cancer		Reference
				O	E	
Colorado plateau, USA	Uranium	1950–77	1180[a]	185	38.4[b]	Waxweiler *et al.* (1981b)
Czechoslovakia	Uranium	1948–73	~300[a]		Ratio[b], 5	Ševc *et al.* (1976); Kunz *et al.* (1978)
Ontario, Canada	Uranium	1955–81	Range, 40–90[c]	119	65.8[b]	Muller *et al.* (1985)
Saskatchewan, Canada	Uranium	1950–80	17	65	34.2[b]	Howe *et al.* (1986)
France	Uranium	1947–83	NA	36	18.8[b]	Tirmarche *et al.* (1984)
Sweden	Iron	1951–76	94	50	12.8[b]	Radford & St Clair Renard (1984)
Sweden	Iron and sulphide	1961–68	163	26	6[d]	Snihs (1973)
Newfoundland, Canada	Fluorspar	1933–81	NA	97	17.4[e]	Morrison *et al.* (1985)

[a]Committee on the Biological Effects of Ionizing Radiations (1980)

[b]Based on national rates

[c]Mean, 33, from Muller *et al.* (1983), based on standard WLM

[d] Based on regional rates

[e]Based on rates for surface workers

NA, not available

Variation in the risks estimated can be attributed in part to uncertainties in the exposure estimates, failure to account for latency, inappropriate choice of comparison group, differences in age distribution and smoking patterns, in distribution of temporal characteristics of exposure and risk and in length of follow-up, as well as to the choice of the model for estimation (Committee on the Biological Effects of Ionizing Radiations, 1980; Radford & St Clair Renard, 1984; Thomas *et al.*, 1985; Howe *et al.*, 1986; International Commission on Radiological Protection, 1987).

Table 19. Summary of risk estimates for lung cancer in undergound miners exposed to radon decay products

Study	Attributable risk/10^6 person-years per WLM[a]	Excess relative risk/100 WLM[a]	Reference
Colorado plateau uranium mining			
Follow-up to 1974	3.52 (0.33)	0.45 (0.04)	Thomas *et al.* (1985) based on Archer *et al.* (1976)
	2.7–8	–	National Council on Radiation Protection and Measurements (1984)
Follow-up to 1977	–	0.31	Whittemore & McMillan (1983)
	2–8	0.3–1.0	International Commission on Radiological Protection (1987)
Follow-up to 1982	–	0.9–1.4	Hornung & Meinhardt (1987)
Czechoslovak uranium miners	16.82 (1.4)	1.92 (0.16)	Thomas *et al.* (1985) based on Ševc *et al.* (1976)
	4.6–22.6	–	National Council on Radiation Protection and Measurements (1984)
	10–25	1.0–2.0	International Commission on Radiological Protection (1987)
Ontario uranium miners	9.59 (2.07)	3.97 (0.86)	Thomas *et al.* (1985) based on Hewitt (1976)
'Special' doses	3.0	0.5	Muller *et al.* (1985)
	2.83 (0.63)	1.07 (0.24)	Thomas *et al.* (1985) based on Muller *et al.* (1983)
'Standard' doses	7	1.3	Muller *et al.* (1985)
	6.35 (1.41)	2.39 (0.53)	Thomas *et al.* (1985) based on Muller *et al.* (1983)
Sasketchewan uranium miners	20.8	3.28	Howe *et al.* (1986)
Newfoundland fluorspar miners	7.75 (1.13)	2.30 (0.34)	Thomas *et al.* (1985) based on Morrison *et al.* (1981)
	17.82 (2.35)	7.98 (1.05)	Thomas *et al.* (1985) based on Committee on the Biological Effects of Ionizing Radiations (1980)
Swedish metal miners			
National survey	3.43 (0.69)	3.03 (0.61)	Thomas *et al.* (1985) based on Snihs (1973)
Malmberget	19.06 (3.62)	4.82 (0.68)	Thomas *et al.* (1985) based on Radford & St Clair Renard (1984)
	19.0	3.6	Radford & St Clair Renard (1984)

[a] In parentheses, standard error

Because of the limited scale of the epidemiological studies of nonoccupational exposure to radon decay products available at the time the reviews were made, the quantification of risk has been based only on data on miners' experience. Of particular note are the studies of uranium miners in Colorado (Lundin *et al.*, 1971; Committee on the Biological Effects of Ionizing Radiations, 1980; Waxweiler *et al.*, 1981b; Whittemore & McMillan, 1983), in Czechoslovakia (Ševc *et al.*, 1976; Kunz *et al.*, 1979) and in Ontario (Chovil, 1981; Muller *et al.*, 1981, 1983, 1985), of Swedish metal miners (Jorgensen, 1973; Axelson & Rehn, 1971; St Clair Renard, 1974; Snihs, 1973; Damber & Larsson, 1982; Jorgensen, 1989; Radford & St Clair Renard, 1984) and of Newfoundland fluorspar miners (Committee on the Biological Effects of Ionizing Radiations, 1980; Morrison *et al.*, 1985).

United Nations Scientific Committee on the Effects of Atomic Radiation (1977): On the basis of an effect assumed to be expressed over a 40-year period, a total lifetime attributable risk of 200–450 lung cancer cases per 10^6 person years per WLM was estimated.

Committee on the Biological Effects of Ionizing Radiations (1980): On the basis of a review of the available literature on exposure of underground miners to radon and its decay products, annual attributable risks of 10 cases per 10^6 person-years per WLM for the age group 35–49, 20 cases per 10^6 person-years per WLM for the age group 50-64 and 50 cases per 10^6 person-years per WLM in the age group 65 and over were estimated.

International Commission on Radiological Protection (1981): On the basis of a review of the available literature on exposure of underground miners to radon and its decay products, and assuming the effect to be expressed over a 30-year period, a total lifetime attributable risk of 150–450 per 10^6 person years per WLM was estimated.

National Council on Radiation Protection and Measurements (1984): On the basis of a review of the available literature on exposure of underground miners to radon and its decay products, an annual attributable risk of 10 per 10^6 person-years per WLM for use in a time- and age-dependent absolute risk model for projection of lifetime risk was estimated.

Thomas et al. *(1985)* (for the Canadian Atomic Energy Control Board): On the basis of analyses of published data from the epidemiological studies of underground miners exposed to radon and its decay products, an incremental relative risk of 0.023 per WLM was presented as the best estimate based on a series of models.

International Commission on Radiological Protection (1987): On the basis of averaging the results of studies of uranium miners in Colorado, Czechoslovakia and Ontario over all ages at start of mining and taking into account a minimum latency of five to ten years, an annual attributable risk of 10 per 10^6 person-years per WLM and an incremental relative risk of 0.01 per WLM were estimated.

(*g*) *Risk modifiers*

A number of factors are of importance or are potential modifiers of the risk of exposure to radon decay products:

Age at observation: An increase in excess risk with increasing age and a fairly constant relative risk for lung cancer are observed in most of the studies of miners considered (Whittemore & McMillan, 1983; Thomas *et al.*, 1985; Howe *et al.*, 1986; International Commission on Radiological Protection, 1987).

Age at first exposure: No consistent effect of age at exposure is seen across the studies of underground miners (Whittemore & McMillan, 1983; Thomas *et al.*, 1985; International Commission on Radiological Protection, 1987).

Duration or dose rate: No effect of duration or dose rate is observed in the Colorado miners study (Whittemore & McMillan, 1983). In Czechoslovakia (Kunz *et al.*, 1979), a higher risk per unit is observed for longer duration and decreased dose rate over time.

Cigarette smoking: Because of the overwhelming importance of cigarette smoking as a risk factor for lung cancer, consideration of the combined effects of smoking and radon decay products is important.

In assessing the consequences of combined exposure to cigarette smoking and radon decay products, consideration must be given to the diverse effects of smoking, as they may modify the relationship between exposure and dose, as well as to the interaction between the two agents in the process of carcinogenesis itself. In comparison with nonsmokers, smokers have greater central deposition of particles, increased airway permeability, slowed mucociliary transport, more airway mucosal oedema, increased mucus layer thickness, on average, secondary to the heightened mucus production of smokers, and more extensive metaplasia and dysplasia of airway epithelium (US Surgeon General, 1984, 1985; Mathé *et al.*, 1986).

Five studies of Swedish metal miners have addressed the interaction of occupational exposure to radon decay products with cigarette smoking. Axelson and Sundell (1978) conducted a case-control study of lung cancer diagnosed in residents of Hammar parish. Occupational exposure was established by review of employee files of the lead and zinc mine within the parish. Smoking status was obtained for the miners by contacting and querying foremen who had been contempories of the subjects. Among the miners, smoking appeared to be protective (adjusted odds radio, 0.5 for smokers, 1.0 for nonsmokers), but the confidence limits around the point estimate were wide (90% CI, 0.1–2.2). [The Working Group noted that the analysis did not fully address interaction because information on smoking was not available for the nonminers.]

Dahlgren (1979) reported an overall four-fold increase in risk for lung cancer in miners who had worked mainly in a sulphide-ore mine in Boliden, northern Sweden, on the basis of a case-control study encompassing 16 cases and 94 controls for the period 1958–77 drawn from a death registry. The risk in the higher exposure category (based on exposure time and mine) was 4.7 and that in the lower exposure category, 2.8, in comparison to nonminers. Among miners in the highest exposure category, four cases and 25 controls were smokers and four cases and 11 controls were nonsmokers, giving an unadjusted risk ratio of 0.4 for lung cancer among smoking *versus* nonsmoking miners.

Radford and St Clair Renard (1984) considered the interaction between cigarette smoking and exposure to radon decay products in their retrospective cohort study of

Swedish iron miners at Malmberget in the municipality of Gällivare. Smoking histories were obtained for all lung cancer cases, generally from next-of-kin or from coworkers. Smoking information was also obtained for a sample of the other cohort members (without lung cancer), either in a survey of active miners conducted in 1972–73 or in a survey of pensioners conducted in 1977. The analysis of interaction between smoking and exposure to radon decay products was based on these data and on a nationwide investigation of smoking among Swedish men conducted between 1963 and 1972. [The Working Group noted that a series of assumptions was made concerning the risks associated with different cigarette smoking patterns, the temporal expression of risk and the assignment of smokers to the various smoking intensity groups.] Expected numbers of cases in the miners were then calculated for smokers and for nonsmokers using the attributable risk method. The observed to expected ratios were 2.9 for smokers (90% CI, 2.1–3.9) and 10.0 for nonsmokers (90% CI, 6.5–14.8). The authors concluded that 'Our report indicates that the absolute risk of lung cancer induced by radon-daughter exposure was only slightly higher for smokers (current smokers and recent exsmokers) than for nonsmokers (those who never smoked and those who had stopped smoking long ago) and the risk of lung cancer in miners relative to nonminers was much higher for nonsmokers than for smokers.' [The Working Group noted that the analysis of interaction required a series of assumptions concerning the distribution and effects of cigarette smoking in the cohort.]

Damber and Larsson (1985) conducted a case-control study in northern Sweden and reported an analysis involving lung cancer cases in the iron mining areas of Kiruna and Gällivare. For each of the 69 cases, one dead control was chosen, and living controls were selected for 60 cases. Subjects were considered to be exposed if they had worked in an underground iron mine for at least one year; years of underground exposure were used in the analysis. Information on cigarette smoking was obtained from the index subjects or their next-of-kin. The results were consistent with a multiplicative interaction for relative risk between the two exposure variables.

Edling (1982) reported a case-control study of lung cancer in the parish of Grängesberg, an iron mining community in Sweden. Employment underground was documented by the mining company, and information on smoking was obtained from next-of-kin. Among the underground miners, the rate ratio for smoking compared with nonsmoking miners was only 2.0 (95% CI, 0.7–5.7).

The interaction between cigarette smoking and exposure to radon decay products in the US Public Health Service study of Colorado plateau uranium miners has been analysed in a number of ways. Early analyses by Archer *et al.* (1973b) and by Lundin *et al.* (1969, 1971), suggesting a multiplicative interaction, have been supported by more recent reports.

Whittemore and McMillan (1983) performed a nested case-control study within the Colorado cohort to examine the effects of exposure to radon decay products and cigarette smoking. For each of 194 cases of lung cancer identified from 1950 through to 1977, four controls were selected from miners matched for birth date. The data were classified by four categories of cigarette consumption and six categories of cumulative WLM. The data were fit initially with a single 23-parameter relative risk model, and the appropriateness of the fit of a variety of other models, including additive, multiplicative and mixture models, was

compared with the saturated model. The additive model was rejected; the data were fit nearly as well by a multiplicative model as by the saturated model.

Hornung and Meinhardt (1987) also used modelling to describe the combined effect of smoking and exposure to radon decay products in this cohort. Their analysis was based on follow-up of the cohort between 1950 and 1982, by which time 256 lung cancer deaths had been identified. Using a power function model for the relative risk, they found that the joint effect of exposure to radon decay products and cigarette smoking was probably slightly less than multiplicative, but greater than additive.

Edling *et al.* (1984, 1986) carried out a case-control study in a rural area of Sweden on the relationship between lung cancer deaths and indoor exposure to radon. The study was limited to subjects aged 40 or more and with a residential history of at least 30 years in the same house prior to death. A two-fold increase in mortality from lung cancer was found for those exposed to more than 50 Bq/m^3, which was not modified when smoking was controlled for. The results also suggested a multiplicative interaction between smoking and exposure to radon.

[The Working Group considered that the epidemiological evidence does not lead to a firm conclusion concerning the interaction between exposure to radon decay products and tobacco smoking. Most of the epidemiological studies involve small numbers of cases, and analytical approaches for assessing interaction have been variable and sometimes inadequate (see Table 20). Analyses of the largest data set, that from the Colorado plateau study, weigh strongly against an additive interaction. Multiplicative and somewhat less than multiplicative models are consistent with these data. The results of other investigations do not consistently indicate either additive or multiplicative interaction.]

(*h*) *Histopathological analysis*

Saccomanno and colleagues have described the histopathological patterns of lung cancer in uranium miners in the Colorado plateau region (Saccomanno *et al.*, 1964, 1971; Archer *et al.*, 1973a, 1974; Saccomanno, 1982). The cases were miners included in the US Public Health Service study and other miners who lived in the Colorado plateau area. The classification of the histopathology was based on either a single pathologist's reading or on the consensus of a panel; 312 cases of lung cancer were analysed among uranium miners. Most of the cases occurred in cigarette smokers; the series included 14 nonsmokers. In the early reports, the majority of the cases were small-cell carcinomas; however, the proportion of this cell type declined from 76% in 1954 to 22% (compared to 17% in nonmining cigarette smokers) in the late 1970s. In nonsmokers, eight cases were small-cell carcinomas and the remaining six were of other cell types (Saccomanno, 1982).

The histopathology of lung cancer in American Indian uranium miners in the Colorado plateau has been reported. Based on record review, Gottlieb and Husen (1982) reported that ten (63%) of 16 cases diagnosed in male Navajo uranium miners at a single hospital were small-cell carcinoma. In a population-based study, Butler *et al.* (1986) reviewed 26 of the 32 lung cancer cases diagnosed among male Navajo uranium miners between 1969 and 1982. A panel of three pathologists classified the cases and found that seven (27%) were small-cell carcinoma (four in smokers), eight were squamous-cell carcinoma (six in smokers), four

Table 20. Results of studies on cigarette use, radon exposure and lung cancer risk in underground miners and the general population

Study area	Design	Results	Comments	Reference
Hammar, Sweden	Cases (29) listed in death register, 1956–76; controls (174) also from register, matched on year of death	Relative risk for mining, 16.6 (90% CI, 7.8–35.3); for smoking among miners, 0.5 (90% CI, 0.1–2.2)	Suggestive of a protective effect of smoking among miners	Axelson & Sundell (1978)
Boliden, Sweden	Cases (16) and controls (94), 1958–77, from a death registry	Crude risk ratio of 0.4 for lung cancer among smoking *versus* nonsmoking miners	Small numbers	Dahlgren (1979)
Malmberget, Sweden	Cohort study of 1415 miners, with 50 lung cancers	O:E, 10.0 for nonsmoking miners, 2.9 for smoking miners *versus* non-miners	Suggestive of submultiplicative model for relative risk, possibly additive	Radford & St Clair Renard (1984)
Kiruna and Gällivare, Sweden	Cases (69) from death register 1972–82; two types of control: alive from general population (60) and deceased from register (67)	Lifetime cigarette use Underground miner: 0 / <150 000 / >150 000 No: 1.0 / 2.4 / 8.4 Yes: 5.4 / 21.7 / 69.7	Consistent with multiplicative relative risk model, although formal testing not presented	Damber & Larsson (1985)
Grängesberg, Sweden	Cases in underground miners (44) listed in death register, 1957–77, and matched controls (44)	Relative risk for smoking among miners, 2.0 (90% CI, 0.7–5.7)	Shorter induction-latency for heavier smokers; suggestive of an additive interaction	Edling (1982)
Colorado, USA	Cohort study of US uranium miners based on follow-up from 1964–67 with 39 lung cancer deaths	Lung cancer rate × 10^4 person-years: Cigarette use: No / Yes Miners: 7.1 / 42.2 Expected[a]: 1.1 / 4.4	Multiplicative combination is suggested	Archer *et al.* (1973b)
Oeland, Sweden	Case-control study of exposure in the home; 23 cases and 202 controls (22 and 178 with smoking habits known, respectively). Exposure considered to have been ≥50 Bq/m³ (0.0135 WL)	Relative risk: Exposed: Yes / No Smoking ever: Yes: 10.3 / 4.1 No: 2.6 / 1.0	Consistent with multiplicative interaction	Edling *et al.* (1984, 1986)

[a]Mortality based on rates in white men in mountain states

were adenocarcinoma (one in smokers) and two were large-cell carcinoma (one in a smoker). Only five nonuranium miners were included, only one of whom had a small-cell carcinoma. They concluded that the proportion of small-cell carcinoma is greater than would be expected from data on nonsmokers. [The Working Group noted that little information was available on histopathological types in Navajo men who were not uranium miners.]

Hóraček *et al.* (1977) reviewed the histological findings of 115 lung cancer cases in Czechoslovak uranium miners and of 326 cases that occurred in men who had not mined uranium. The proportion of small-cell cancer was greater in the uranium miners (54% *versus* 42%) and the proportion of adenocarcinoma was smaller (4% *versus* 13%). The proportion of epidermoid carcinoma was the same in the two groups (35%).

Chovil (1981) reported that histopathology was available from clinical records for 91 cases of lung cancer in Ontario uranium miners; 47 (52%) were small-cell carcinoma.

The histopathology of 45 lung cancer cases (42 smokers) among uranium miners in New Mexico, USA, has been described (Butler *et al.*, 1985). The consensus readings of a panel of three pathologists were 28 cases (62%) of small-cell carcinoma, 15 of squamous-cell carcinoma, one of adenocarcinoma and one of large-cell carcinoma.

Histopathology has also been reported in some studies of Swedish metal miners. Of 15 lung cancer cases (14 smokers) identified among underground iron-ore miners in northern Sweden, 11 were squamous-cell carcinoma and four were oat-cell cancer (27%) (Jorgensen, 1984). Of 25 cases (23 smokers) of lung cancer in underground iron miners in northern Sweden, 11 (44%) were small-cell carcinoma, 11 were squamous-cell carcinoma and three were adenocarcinoma (Damber & Larsson, 1982). The histopathological distribution of 42 cases in underground iron miners in the case-control study in northern Sweden (Damber & Larsson, 1985) was 12 (29%) small-cell carcinoma, 23 squamous-cell carcinoma, four adenocarcinoma and three other or undefined types. The histopathology of 36 cases among Swedish iron miners was reviewed; 26 cases (72%), including three in nonsmokers, were small-cell carcinoma and ten cases, including one in a nonsmoker, were squamous-cell carcinoma (Edling, 1982).

Wright and Couves (1977) described the histopathology of 29 cases of lung cancer among fluorspar miners in Newfoundland, Canada, as classified by sputum cytology. Two (7%) were small-cell carcinoma, 26 were squamous-cell carcinoma and one was an adenocarcinoma. [The Working Group noted that a histopathological distribution based on sputum cytology may be biased and may overrepresent centrally arising tumours.]

Small-cell carcinomas (25%) have also been seen among patients with lung cancer who lived in nonwooden houses (Table 21) (Damber & Larsson, 1986).

Table 21. Distribution of cell types among lung cancer patients living in nonwooden houses[a]

Cell type	Years in nonwooden houses					
	0		1–20		>20	
	No.	%	No.	%	No.	%
Small-cell carcinoma	81	24	51	27	18	31
Squamous-cell carcinoma	159	46	90	47	36	62
Adenocarcinoma	58	17	21	11	2	3
Other types and not classified	43	13	28	15	2	3
Total	341		190		58	

[a]From Damber and Larsson (1986)