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Abundant epidemiological data from underground miners confirm that radon decay products (progeny) are carcinogenic, although the evidence is less conclusive on the quantitative risks of these exposures, especially for indoor air (1). The imprecision results principally from differences between exposures in mining and domestic environments and from uncertainties about the interaction between smoking and exposure to radon progeny.

Experimental animal studies of radon-induced lung cancer are particularly valuable for understanding the carcinogenicity of human radon exposures in the home and in the workplace. Animals can be exposed to a variety of agents under carefully controlled conditions and then sacrificed for the study of developing lesions or held for their life span for tumor development. The doses to critical cells in the respiratory tract can be determined, and these in turn can be related to doses to critical cells in the respiratory tract of humans exposed to similar aerosols.

The study of radon-induced mutations and changes in expression of oncogenes and tumor-suppressor genes as well as growth factors and growth factor receptors during tumor progression in animals also provides valuable evidence on the underlying mechanisms of radon carcinogenesis. This evidence, particularly that of the efficiency for oncogenic transformation at low dose rates, is crucial to the determination of the risk of lung cancer from exposure to indoor levels of radon.

This review of animal health effects data emphasizes the carcinogenicity of radon exposures in rats; mechanistic data on radon-induced lung tumors in rats are currently sparse and are not reviewed here.

HEALTH EFFECTS DATA

These radon health effects data, developed primarily in adult male animals, are provided by the Pacific Northwest Laboratory (PNL) and the Compagnie Générale des Matières Nucleaires (COGEMA) laboratory in France (2). Approximately 800 Syrian Golden hamsters, 6,000 SPF Wistar rats, and 100 beagle dogs were exposed to mixtures of radon, radon progeny, diesel engine exhaust, uranium ore dust, and cigarette smoke in PNL studies; about 10,000 SPF Sprague-Dawley rats were exposed to mixtures of radon, radon progeny, ambient (outdoor) aerosols, and cigarette smoke in COGEMA studies. Additional French radon carcinogenesis modeling studies employed intramuscular injections of the promoter 5,6-benzoflavone (3). The rat data from the two laboratories are discussed as a whole, primarily because of their similarity; emphasis, however, is placed on the PNL data. Hamster and dog data,

discussed only briefly here, are presented in greater detail in the report to the U.S. Department of Energy (2).

Major biological effects produced in the radon studies were respiratory tract tumors [adenomas, bronchioloalveolar (BA) carcinomas or adenocarcinomas, epidermoid carcinomas, adenosquamous carcinomas, and sarcomas], pulmonary fibrosis, pulmonary emphysema, and life-span shortening (2). Appreciable fibrosis, emphysema, and life-span shortening, although somewhat species dependent, did not occur at exposure levels less than 3.5 J h m^{-3} (1000 WLM[1]). However, excess respiratory tract tumors were produced in rats at exposures well below 0.35 J h m^{-3} (100 WLM), even at levels comparable to typical life-span exposures in homes. Further, tumors were produced in exposures to radon decay products alone; thus, associated exposures to other irritants, such as uranium ore dust or cigarette smoke, are not necessary for carcinoma development.

With a few exceptions, the percent incidence of adenomas and sarcomas was well below 10%. A decrease in exposure rate at a given exposure level not only increased the overall incidence of lung tumors but specifically increased the incidence of epidermoid carcinomas. These data are exampled in Table I for fixed exposure levels at two exposure rates in a subset of 605 rats. Protraction of exposures in rats also produced a significantly higher incidence of multiple primary lung tumors (more often of a different type than the same types) and fatal primary lung tumors. Most (>70%) epidermoid carcinomas but only about 20% of adenocarcinomas were classified as fatal. Finally, most (~80%) radon-induced lung tumors in rats are considered to originate peripherally and to occur at the bronchiolar-alveolar junction. The remaining 20% are considered to be centrally located (bronchi associated); the actual percent depends somewhat on exposure rate and possibly on exposure level (4).

Extrapulmonary lesions, including tumors, were produced primarily in the nose, particularly with high unattached fractions of radon decay products. Significant excess nonrespiratory neoplasms associated with radon exposure were noted primarily in the kidneys; however, neoplastic lesions in nonrespiratory tissues were incidental findings and therefore may have been underestimated in both control and exposed animals.

Finally, other experiments were performed to determine if prenatal effects could be produced by prolonged inhalation exposures to high concentrations of radon progeny throughout gestation (5). Neither teratologic nor reproductive effects were produced when pregnant SPF Sprague-Dawley rats were exposed to about 10,000 times typical annual radon-progeny levels in houses. Thus, the human fetus is not likely to suffer teratologic effects from typical indoor radon levels.

The major factors found to influence the tumorigenic potential of radon exposures in laboratory rats include radon-progeny cumulative exposure, exposure rate, unattached fraction, and associated cigarette-smoke exposures (2). The respiratory tract cancer risk increases with increase in radon-progeny cumulative exposure and unattached fraction and, as noted previously, decreases with increase in radon-progeny exposure rate. The increased risk with high unattached radon progeny is particularly relevant to indoor radon exposures where the unattached levels are generally much higher than those in underground mines. The influence of associated cigarette-smoke

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[1]Working level (WL) is defined as any combination of short-lived radon decay products in 1 liter of air resulting in the ultimate emission of 1.3 x 10^5 MeV of potential alpha energy (1 WL = 2.08 x 10^{-5} J m^{-3}). Working-level month: exposure equivalent to 170 hours at 1-WL concentration (1 WLM = 3.5 x 10^{-3} J h m^{-3}).

TABLE I
Percent Incidence of Primary and Fatal Lung Tumors
in Rats Versus Radon-Progeny Exposure Rate and Level[a]

Exposure (WLM)	320	640	1280	2560	5120
At 500 WLM wk^{-1}					
No. animals examined	131	70	38	38	41
Adenoma	5	3	0	3	2
Adenocarcinoma	8	7	26	24	44
Epidermoid carcinoma	1	0	0	3	2
Adenosquamous carcinoma	0	0	3	0	0
Sarcoma	0	0	0	3	2
Fatal lung tumors	2	1	5	11	15
Animals with lung tumors (%)	15	14	29	32	49
At 50 WLM wk^{-1}					
No. animals examined	127	64	32	32	32
Adenoma	5	3	[22]	9	[22]
Adenocarcinoma	5	[20]	41	41	53
Epidermoid carcinoma	1	3	[13]	[47]	[44]
Adenosquamous carcinoma	1	3	9	[9]	3
Sarcoma	1	2	3	0	0
Fatal lung tumors	2	6	[22]	[50]	[44]
Animals with lung tumors (%)	10	[28]	[66]	[69]	[75]

[a] 15 mg m^{-3} ore dust exposures accompanied radon and radon progeny exposures; data in brackets at 50 WLM wk^{-1} are significantly ($p < 0.05$) higher than corresponding data at 500 WLM wk^{-1}; see text for WL and WLM definitions.

exposures depends in part on the temporal sequence of radon progeny and cigarette-smoke exposures. In the COGEMA experiments, the risk was synergistically increased when smoke exposures followed completed radon exposures, but the risk remained unchanged from radon-only exposures when the exposure sequence was reversed (6). The promotional effect of cigarette smoke was also seen for the preneoplastic lesion adenomatosis but not for lung tumors in recent PNL serial-sacrifice initiation-promotion-initiation (IPI) studies (7). The life-span IPI tumor data are currently being analyzed, and preliminary evidence suggests antagonism. Earlier PNL dog experiments (8) and recent Harwell mice experiments (9) also showed antagonism in tumor

production with alpha-particle radiation and cigarette-smoke exposures, possibly as a result of overly high radiation doses that obscured the promotional effect of cigarette smoke.

Except for the greater prevalence of solid alveolar tumors and BA carcinomas and the absence of oat-cell carcinomas observed in rats, the tumor data in rats and humans are quite similar. Regional differences in tumor formation are explained, in part, by dose differences. The doses to rat terminal bronchioles and alveoli are generally quite high in comparison to these regions in humans [A. C. James (PNL), personal communication]. On the other hand, doses to human proximal bronchi are generally quite high compared with those in the rat; thus, one might postulate that regions of tumor development coincide with regions of high dose.

STATISTICAL MODELING

Statistical analyses of PNL and COGEMA radon lung tumor data in rats have been used to model the hazard using the Weibull function for the baseline risk (10, 11). Figure 1 summarizes the results of incidental analyses of PNL data based on the linear relative risk model. Similar to the analysis of the COGEMA data, there is little indication of a decrease in risk per unit exposure with increasing total exposure, even to very high exposure levels. The analysis clearly shows the influence on risk of exposure rate; except at 1.1 J h m^{-3} (320 WLM), the corresponding exposure-rate data are significantly different from each other.

The estimated linear-lifetime lung tumor risk coefficient, based on the combined exposure-rate data, was about 0.086 per J h m^{-3} (300 per million rats per WLM) for adenomas and carcinomas combined. Excluding adenomas, the risk is reduced to about 0.071 per J h m^{-3} (250 per million rats per WLM). These values may be compared to the overall (smokers and nonsmokers) BEIR IV value of 0.10 per J h m^{-3}

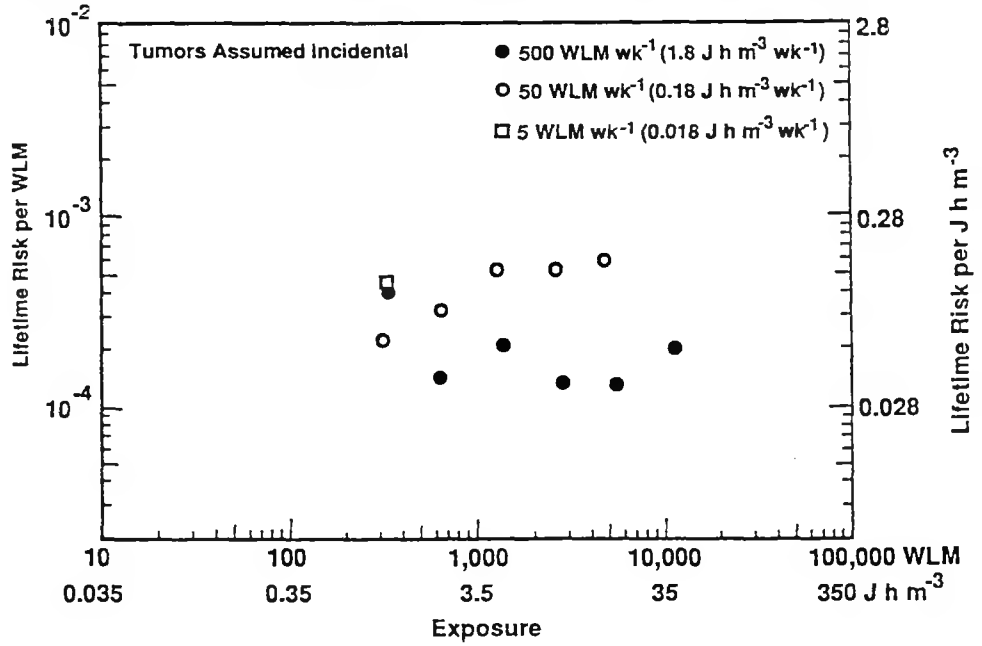

Figure 1. Lifetime risk coefficients for radon-progeny exposure of rats (modified from Figure 1, reference 10).

(350 per million persons per WLM) and 0.040 per J h m^{-3} (140 per million persons per WLM) for nonsmoking males (1). Estimates from rats, therefore, are comparable to those obtained from human studies. Analyses based on the assumption that tumors are fatal produce risk coefficients about half as large. The lowest exposure-rate data [0.018 J h m^{-3} wk^{-1} (5 WLM wk^{-1})] in Figure 1 suggest that the exposure-rate effect (but not the risk) tapers off at lower exposure levels; however, the shape of the risk curve for the much lower indoor radon-progeny exposure rates is still in question.

CARCINOGENESIS MODELING

The two-mutation (recessive oncogenesis) model of Moolgavkar and Knudson (12) was employed to model a PNL tumor data set similar to that used in the statistical analyses by Gilbert. This model postulates transitions from a normal cell to an intermediate cell to a malignant cell with quantifiable transition rates and takes account of the growth characteristics of the normal cell and intermediate cell populations. The model describes the rat lung cancer data well (13). Briefly, the findings are that the first mutation rate is very strongly dependent on the rate of exposure to radon progeny and the second mutation rate much less so, suggesting that the nature of the two mutational events is different. The model predicts that: (1) radon doubles the background rate of the first mutation at an exposure rate of approximately 0.005 J h m^{-3} wk^{-1} (1.35 WLM wk^{-1}), an exposure rate definitely in the range of miner exposures; (2) radon doubles the background rate of the second mutation at an exposure rate of about 1.4 J h m^{-3} wk^{-1} (400 WLM wk^{-1}); consequently, the hypothesis that radon has *no* effect on the second mutation rate cannot be rejected; and (3) the net rate of intermediate cell growth is doubled at about 0.12 J h m^{-3} wk^{-1} (35 WLM wk^{-1}). The model also predicts a drop in hazard after radon exposures cease, paralleling the exposure-rate effect noted previously, and an optimal exposure schedule for producing tumors. In the latter case, fractionation of exposure is more efficient in producing tumors, but further fractionation leads to a decreased efficiency of tumor production. The implications of these findings for human risk assessment are somewhat uncertain at this time.

CONCLUSIONS

Our broad multilevel approach to radon cancer risk assessment includes mechanistic, animal, dosimetric, statistical, and carcinogenesis modeling data to infer risks to humans exposed in occupational and residential settings. The similarity of current adult rat and underground miner exposure-response data suggests that the rat model is particularly valuable for reducing scientific uncertainties in the human data base, particularly in regard to the complex interactions of radon and cigarette-smoke exposures and the risks associated with childhood exposures. The effort to measure radon levels in schools in the United States demonstrates the concern for the latter type of exposures, yet the observed drop in hazard with time since exposure would tend to discount early (childhood) exposures. The rat model is also valuable for delineating the mechanisms of radon carcinogenesis, as evidenced by recent studies on oncogene and growth factor/receptor involvement in radon-induced lung tumors in rats (14, 15).

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