

● Inhalation Hazards to Uranium Miners

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This project is investigating levels of uranium mine air contaminants, using both large and small experimental animals to model human respiratory system disease. Lung cancer and deaths by degenerative lung disease have reached epidemic proportions among uranium miners, but the cause-effect relationships for these diseases are based on inadequate epidemiological data. This project identifies agents or combinations of agents (both chemical and radiological) and their exposure levels that produce respiratory tract lesions, including respiratory epithelial carcinoma, pneumoconiosis and emphysema.

Small-Animal Studies

Approximately 1100 male specific-pathogen-free Wistar rats are currently on study; the 4000 and 5000 Series experiments (Tables 1 and 2) are designed to clarify the roles of unattached RaA daughters, and the degree of radon daughter disequilibrium, on the development of respiratory system disease. The 6000 and 7000 Series experiments (Table 3) are designed to develop the relationships between response and exposure to radon daughters (at two rates of exposure) and carnotite uranium ore dust. The exposures of 6000 and 7000 Series animals are currently in progress; the exposures of 4000 and 5000 Series animals are completed; a few of the animals are still living.

TABLE 1. Radon-Daughter Unattachment Fraction Study in Rats (4000 Series experiments).

Exposure Regimen ^(a)	Total Exposure, WLM ^(b)
500 WL Radon Daughters Low RaA Unattachment (~2%) ~15 mg/m ³ Uranium Ore Dust	5120
500 WL Radon Daughters Intermediate RaA Unattachment (~10%) ~0.7 mg/m ³ Uranium Ore Dust	5120
500 WL Radon Daughters High RaA Unattachment (~24%) ~0.4 mg/m ³ Uranium Ore Dust	5120
Controls	

(a) 32 animals in each group, exposed 90 hr/wk

(b) Working Level (WL) is defined as any combination of the short-lived radon daughters in 1 liter of air that will result in the ultimate emission of 1.3×10^5 MeV of potential α -energy. Working Level Month (WLM) is an exposure equivalent to 170 hr at a 1-WL concentration.

TABLE 2. Radon-Daughter Disequilibrium Study in Rats (5000 Series experiments).

Exposure Regimen ^(a) Daughter Equilibrium Ratios				Total Exposure, WLM ^(b)
Rn	RaA	RaB	RaC-C'	
1	0.9	0.4	0.2	5120
1	0.5	0.07	0.01	5120
Controls				

(a) 32 animals in each group, exposed 90 hr/wk at 500 WL and 15 mg/m³ uranium ore dust

(b) Working Level (WL) is defined as any combination of the short-lived radon daughters in 1 liter of air that will result in the ultimate emission of 1.3×10^5 MeV of potential α -energy. Working Level Month (WLM) is an exposure equivalent to 170 hr at a 1-WL concentration.

We have concluded that the most significant lesions related to radon daughter and carnotite ore-dust exposures in the 4000 Series experiments are malignant tumors of the respiratory tract. Histopathologic data for these tumors in the low and high RaA-unattachment groups are shown in Table 4. The tissues of animals of the intermediate RaA unattachment group, and for the 5000 Series experiments, are currently undergoing histopathologic examination.

The data in Table 4 suggest that a low RaA unattachment fraction (~2%) or high concentration of dust (~15 mg/m³) is associated with a higher risk of malignant lung tumor development than a high RaA unattachment fraction (~24%) or low dust concentration (~0.4 mg/m³). However, this interpretation must be delayed until a

TABLE 3. Exposure-Response Relationship Study for Radon-Daughter Carcinogenesis in Rats (6000 Series experiments).

Number of Animals ^(a)	Exposure Regimen ^(b,c)	Total Exposure, WLM ^(d)
32	1000 WL Radon Daughters 15 mg/m ³ Uranium Ore Dust	10,240
32	1000 WL Radon Daughters 15 mg/m ³ Uranium Ore Dust	5120
32	1000 WL Radon Daughters 15 mg/m ³ Uranium Ore Dust	2560
32	1000 WL Radon Daughters 15 mg/m ³ Uranium Ore Dust	1280
64	1000 WL Radon Daughters 15 mg/m ³ Uranium Ore Dust	640
128	1000 WL Radon Daughters 15 mg/m ³ Uranium Ore Dust	320
32	Controls	

(a) Number of animals is sufficient to detect the predicted incidence of lung tumors at the 0.05 to 0.1 level of significance, assuming linearity of response between 0 and 9200 WLM (see footnote d), and 0.13% spontaneous incidence.

(b) Exposure rate, 90 hr/wk; planned periodic sacrifice

(c) Study will be repeated @ 100 WL rate (without periodic sacrifice) to augment previous limited exposure-rate data (7000 series experiments).

(d) Working Level (WL) is defined as any combination of the short-lived radon daughters in 1 liter of air that will result in the ultimate emission of 1.3×10^5 MeV of potential α -energy. Working Level Month (WLM) is an exposure equivalent to 170 hr at a 1-WL concentration. Previous exposure at 900 WL for 84 hr/wk to 9200 WLM produced a 60% incidence of carcinoma.

TABLE 4. Current Summary of Malignant Respiratory Tract Tumors (4000 Series experiments).

Malignant Respiratory Tract Tumors	RaA Unattachment Groups			
	Low	Intermediate	High	Controls
Lung				
Epidermoid Carcinoma	9	..	2	0
Adenocarcinoma	9	..	5	1
Malignant Mesothelioma	1	..	0	0
Total Number of Rats	16 ^(a)	..	7	1
Nose				
Nasal Carcinoma	1	..	2	0
Total Number of Rats with Respiratory Tumors	17	..	g ^(b)	1

(a) Two rats had both epidermoid carcinomas and adenocarcinomas, and one rat had two types of adenocarcinomas.

(b) One rat had both a lung tumor and a nasal tumor.

competing risk analysis is performed on the data. (The mean survival times of the exposed animals were significantly [$P < 0.001$] reduced from those of controls and was shortest in the high RaA unattachment group of animals.) Although of doubtful significance, the high RaA unattachment

exposure was associated with a higher incidence of nasal carcinoma.

Large-Animal Studies

Thirty-five beagle dogs are currently on study to determine the pathogenic role of inhalation exposure to carnotite uranium ore dust. We are particularly interested in clarifying the role of the ore dust in the production of the massive pulmonary fibrosis observed in an earlier study, in which beagle dogs were exposed to radon daughters and mixtures of uranium ore dust and cigarette smoke. The present study (chronic, head-only exposures) began when the dogs were about 2½ years old. Along with routine physical examinations and periodic hematologic and clinical chemistry measurements, histopathologic, morphometric and pulmonary function evaluations were conducted on these dogs. The histopathologic and morphometric data from sacrificed animals are shown in Table 5.

The most consistent pulmonary-function change attributed to carnotite uranium-ore-dust exposure (at ~15 mg/m³, for 4 hr/day, 5 days/wk) is an increased slope of the single-breath N₂ washout curve, suggesting an uneven distribution of ventilation. This change was observed in dogs exposed for less than 1 year and continued through 4 yr of exposure. Measurements of pulmonary resistance, made after 27, 40 and 47 mo exposure, showed slight age-related changes and increasing difference between control and exposed animals with duration of exposure. These two changes are suggestive of bronchitis, similar to the "industrial" bronchitis of mine workers. Along with a suggestion of change in the dynamic pulmonary compliance values, these findings indicate changes in the distal airways of the dogs' lungs.

The most notable pulmonary lesions observed in dogs exposed for up to 4 yr are vesicular emphysema, peribronchiolitis and focal pneumoconiosis. The degree of pulmonary interstitial fibrosis (other than that associated with the focal pneumoconiosis-related changes) was slight, and no dose response was evident. This is in contrast to the marked pulmonary fibrosis found, in earlier studies, in the lungs of dogs following approximately 3 yr exposure to radon daughters and carnotite ore dust, suggesting a more rapid development of this lesion when radon daughters are combined with carnotite ore dust.

Lesions of the major airways and upper respiratory tract, when present, were minimal in severity. Pulmonary vesicular emphysema, present in all but one of the examined dogs, was dose-related, in that

TABLE 5. Degree of Severity of Selected Pulmonary Changes Resulting from Chronic Inhalation Exposure of Dogs to Uranium Ore Dust.

Dog Number	Duration of Exposure, mo	Degree of Severity ^(a)			
		Pulmonary Vesicular Emphysema		Focal Pneumoconiosis ^(b)	Peribronchiolitis ^(b)
		Subjective ^(b)	Morphometric ^(c)		
1670	12	1	57	2	1
1675	12	1	59	2	1
1679	12	1	64	1	0
1467	20	1	76	2	0
1462	26	1-2	97	3	2-3
1469	26	1-2	60	2-3	1
1468	37	1	58	2-3	1
1493	37	1-2	77	2-3	1
1499	37	1-2	90	2-3	1
1473	48	2	90	2	1
1464	48	2	87	2-3	1
1478	48	2	82	2	1

(a) Code: 1 = Barely perceptible
 2 = Readily apparent
 3 = Obvious change

(b) Subjective grading based on light microscopy evaluation (all lung lobes)

(c) Mean chord length across alveoli (μm , morphometric evaluation; right diaphragmatic lobe only)

it was present to only a slight degree in dogs exposed for less than 3 yr, increasing in severity thereafter.

Morphometric measurement data confirmed the value of the histopathologic system for grading the degree of emphysema.