

• 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. Histopathologic data from rats are shown for approximately 300- to 10,000-working-level-month (WLM) radon-daughter exposures. Exposure of male rats to radon daughters and uranium ore dust continues, along with exposure of male and female beagle dogs to uranium ore dust alone.

Small-Animal Studies

Approximately 1000 male, specific-pathogen-free, Wistar rats are currently on study; the 6000 and 7000 Series experiments (Table 1) are designed to develop the relationships between response and exposure to radon daughters (at two rates of exposure) and carnotite uranium ore dust.

The 8000 Series experiments (Table 2) are designed to extend the exposure-response relationships to levels appropriate to current conditions in the mines and to lifetime environmental exposures. The 9000 Series experiments (Table 3) continue the "low-dose" studies at exposure rates comparable to former occupational working levels (10 WL). They will help to further evaluate the hypothesis that the tumor probability per WLM exposure increases with decrease in exposure and exposure rate. In addition, concurrent exposure to varying levels of uranium ore dust tests the hypothesis that irritants (both specific and nonspecific) act synergistically with radiation exposures, the synergism increasing with decrease in exposure level. The exposures of 9000 Series animals are currently in progress; the exposures of 6000, 7000 and 8000 Series animals are completed; some of the 8000 Series animals are still living.

We have concluded that the most significant lesions related to radon-daughter and carnotite-ore-dust exposures in the 6000 Series experiments are neoplastic and non-neoplastic lesions of the respiratory tract. Histopathologic data for these lesions in serially sacrificed animals

TABLE 1. Exposure-Response Relationship Study for Radon-Daughter Carcinogenesis in Rats (6000 and 7000 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	160

(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 an 80% incidence of carcinoma.

TABLE 2. Low-Exposure Response Relationship Study for Radon-Daughter Carcinogenesis in Rats (8000 Series Experiments).

Number of Animals ^(a)	Exposure Regimen ^(b)	Total Exposure, WLM ^(c)
64	100 WL Radon Daughters 15 mg/m ³ Uranium Ore Dust	640 ^(d)
64	100 WL Radon Daughters 15 mg/m ³ Uranium Ore Dust	320 ^(d)
160	100 WL Radon Daughters 15 mg/m ³ Uranium Ore Dust	160
352	100 WL Radon Daughters 15 mg/m ³ Uranium Ore Dust	80
448	100 WL Radon Daughters 15 mg/m ³ Uranium Ore Dust	40
512	100 WL Radon Daughters 15 mg/m ³ Uranium Ore Dust	20
160	Controls	

(a) Number of animals is sufficient to detect lung tumors at the 0.05 to 0.1 level of significance, assuming linearity of response between 0 and 640 WLM (see footnote c), and 0.13% spontaneous incidence.

(b) Exposure rate, 90 hr/wk; planned periodic sacrifice of 32 animals from group

(c) Recent exposures indicate a tumor incidence of 16% at 640 WLM. 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.

(d) Repeat exposure is for normalization with Table 3 data.

were shown in the 1983 Annual Report. These data indicated that the earliest lung cancers generally occurred approximately 1 year following completion of ex-

TABLE 3. Ultralow Exposure Rate Study for Radon-Daughter Carcinogenesis in Rats (9000 Series Experiments).

Number of Animals ^(a)	Exposure Regimen ^(b)	Total Exposure, WLM ^(c)
64	10 WL Radon Daughters 15 mg/m ³ Uranium Ore Dust	320
64	10 WL Radon Daughters 3 mg/m ³ Uranium Ore Dust	320
352	10 WL Radon Daughters 15 mg/m ³ Uranium Ore Dust	80
352	10 WL Radon Daughters 3 mg/m ³ Uranium Ore Dust	80
512	10 WL Radon Daughters 15 mg/m ³ Uranium Ore Dust	20
512	10 WL Radon Daughters 3 mg/m ³ Uranium Ore Dust	20
96	Controls	

(a) Number of animals is sufficient to detect lung tumors at the 0.05 to 0.1 level of significance, assuming linearity of response between 0 and 640 WLM (tumor incidence is approximately 16% at 640 WLM), and 0.13% spontaneous incidence.

(b) Exposure rate, 90 hr/wk; planned periodic sacrifice of 32 animals in each group

(c) Working level (WL) is defined as any combination of the short-lived 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.

posures. At exposure levels less than 1280 WLM, no lung cancers were observed earlier than 18 months after exposure.

The current summary of tumors primary to the rat lung in the 6000 Series experiments is shown in Table 4.

TABLE 4. Current Summary of Primary Tumors of the Respiratory Tract (6000 Series Experiments).

Nominal Exposure, WLM	Animals Examined	Lung Tumors							No. of Animals with Respiratory Tract Tumors
		Nasal Carcinoma	Adenoma	Adenocarcinoma	Epidermoid Carcinoma	Adenosquamous Carcinoma	Sarcoma ^(a)		
10,240	52	3	2	27	7	3	2	33	
5120	41	1	1	17	1	0	2	21	
2560	38	0	0	10	1	0	1	12	
1280	38	2	0	10	0	1	0	12	
640	70	1	2	5	0	0	0	8	
320	68	0	6	1	1	0	0	8	
Controls	45	0	0	0	0	0	0	0	

(a) Sarcomas include 2 hemangiosarcomas, 1 mesothelioma, 1 undifferentiated sarcoma, and 1 malignant mixed lung tumor.

Large-Animal Studies

Eighteen (nine exposed and nine controls) of 35 beagle dogs remain on study to determine the pathogenic role of carnotite uranium ore dust in inhalation exposure. We are particularly interested in clarifying the role of ore dose 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, radiometric, morphometric, renal and pulmonary-function evaluations were conducted on these dogs.

The most notable pulmonary lesions observed in dogs exposed for up to 4 years (a comparable exposure time to the earlier

study) are vesicular emphysema, peribronchiolitis and focal pneumoconiosis. These lesions, described in the 1981 Annual Report, are in contrast to the comparatively more severe lesions observed in the earlier study, in which beagle dogs were exposed to mixtures of radon daughters, uranium ore dust and cigarette smoke.

Renal function was evaluated on six uranium-ore-dust-exposed and six sham-exposed dogs following 6 years of exposure for 20 hours/week to 15 mg/m³ uranium-ore-dust concentrations (1983 Annual Report). With the exception of elevated glucose levels, results of a battery of tests were equivalent for the exposed and sham-exposed dogs, leading to the conclusion that kidney function had not been appreciably compromised by 6 years exposure to uranium ore dust.

The animals, to date, have received 7½ years exposure to uranium ore dust.