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EFFECTS FROM CHRONIC INHALATION OF ASBESTOS PIPE-COVERING DUST IN RATS AND HAMSTERS

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ABSTRACT

Rats and hamsters were exposed to the dust of pulverized asbestos pipe covering at an average concentration of 85 mg/M^3 for 6 hours per day, 5 days per week for 7 months followed by a lifetime observation period.

In rats, the pulmonary responses were alveolar adenomatous proliferation, non-progressive fibrosis, squamous metaplasia and a substantial incidence of pulmonary carcinoma formation.

A smaller group of hamsters exposed under these conditions experienced an earlier onset of mortality than control hamsters not subjected to the exposure regimen. Although this prevented conclusive evaluation of the pulmonary response in this species, there were no pulmonary neoplasms noted in the surviving hamsters.

INTRODUCTION

Asbestos materials, primarily chrysotile, crocidolite, and amosite, are used extensively as thermal insulation materials.[1] Many industrial products worldwide rely increasingly on asbestos and the variety of its uses. At the same time, asbestos is also being perceived as a major health hazard.

Asbestos dust exposure is now widely recognized as an important etiological factor in pulmonary fibrosis,[2,3,4] respiratory cancers,[5-9] and malignant mesothelial tumors.[10-16] However, the precise mechanisms of the causal relationships have not yet been clarified although many theories have been proposed. Several factors in the carcinogenic response to asbestos have been identified: (1) the action of the fiber it self due to its particular geometry,[16,17] (2) trace metals associated with the fiber (some of which are known to be carcinogenic themselves),[18,19] (3) polycyclic aromatic hydrocarbons associated with the fiber,[20] (4) other carcinogenic agents adsorbed onto the asbestos during milling, handling, mining, etc. and carried on the asbestos fiber into the body,[19] and (5) cigarette smoke in conjunction with asbestos exposure.[7] Considering these factors, the theories basically view asbestos fiber as a carcinogen or as a carrier of a carcinogen.

Most of the asbestos inhalation experiments to date were conducted using relatively pure mineralogical types of dust. The findings in rats and hamsters exposed to asbestos dusts generated from prefabricated asbestos pipe covering are presented in this paper. The duration of exposure was 6 hours per day, 5 days per week for 7 months followed by observation for the life of the animals.

MATERIAL AND METHODS

Material

Asbestos dust was prepared by pulverizing a section of a prefabricated asbestos air-cell pipe covering into coarse powder with an industrial hammer mill for 5 minutes. The coarse powders were further reduced to micron and submicron sizes in a ceramic ball mill running for 48 hours. The final dust sample consisted of 30-40% of noncrystalline and approximately 60% of crystalline materials as determined by X-ray diffraction analysis. The crystalline components consisted of approximately 50% asbestos form materials (chrysotile), 5% Fe_3O_4, 5% $Mg(OH)_2$ and 5% MgO. Atomic emission spectrographic analysis of a representative sample revealed the presence of various minerals as shown in Table 1.

Dust Atmosphere Generation

The asbestos dust atmosphere was generated by using an air elutriator as shown in Fig. 1. The elutriator consisted of a 90 x 10 cm Pyrex tube. The bottom of the tube was sealed with a rubber diaphragm attached to an air vibrator. The powder was poured through the opening on top of the tube onto the rubber diaphragm. The powder was then churned up by the vibrating diaphragm and was carried upward by a swirling air current emerging from two air nozzles located

just above the diaphragm. The quantity of fine dust to be introduced into the exposure chamber could be regulated by adjusting the vibration frequency of the diaphragm and the volume of air ejecting through the dust cloud. For a 6 hour exposure period 20 grams of powder were initially placed in the dust generator. Additional 10-gram portions of powder were added twice daily to maintain a fairly constant level of dust in the chamber atmosphere. The coarse residue was discarded at the end of each experimental day.

Chamber Dust Concentration Analyses

The concentration of asbestos dust in the chamber atmosphere was determined gravimetrically using a membrane filter-sampler technique. Two open-face dust samplers were placed in the center of the exposure chamber just above the animal holding cages. A third sampler was placed within an empty cage surrounded by other cages containing animals. An air sample was drawn at the rate of 8.5 liters per minute for 5 to 10 minutes through a 47 mm diameter membrane filter (Metricel GA-4) of 0.8 µm pore size. The asbestos dust retained by the filter was weighed so that the dust concentration, in terms of milligrams per cubic meter of air, could be determined.

Particle Size Distribution Analyses

The particle size distribution of the airborne asbestos dust in the chamber was monitored using a light scattering particle counter. Dust in air samples drawn from the center of the chamber was analyzed for particle size distribution. The dust trapped in a membrane filter sampler was dispersed in a suitable mounting medium and counted automatically with a phase contrast microscope interfaced with an automatic scanning image analyzer. The digital outputs from the particle analyzer or image analyzer were computerized and the number-length-mean diameter of each sample was calculated. The dusts trapped in the membrane filter sampler were subjected to scanning electron microscopy to determine the particulate and fiber content of the sample.

Experimental Design

50 male Sprague-Dawley Specific Pathogen Free (SPF) derived rats of Spartan substrain and 15 male Golden Syrian hamsters were exposed to the asbestos dust. The duration of exposure was 6 hours per day, 5 days per week for a total of 150 exposures in 7 months. The exposures were conducted in a one-cubic meter stainless steel and glass chamber under dynamic airflow conditions. During the exposure, the animals were housed individually in wire gauze cylinders 3 inches in diameter and 12 inches long. The cylinders could be piled

together up to 5 layers deep without affecting the distribution of dust to the animals. At the end of each exposure day, the animals were removed from the cylinders and housed in gang cages with food and water. A comparable group of 50 rats and 15 hamsters was maintained in an animal holding room to serve as controls. These animals were not placed in individual cylinders daily but were deprived of food and water on a schedule identical to that of the exposed animals.

At the termination of the 7-month exposure period, the exposed animals were housed in a holding room with the control animals.

Animal Observation

During the exposure period all animals were observed for evidence of ocular, nasal and respiratory irritation. Body weights were determined once a week for approximately 8 months (7 exposure months and 1 month post-exposure) and monthly thereafter until all animals died. The body weight data were analyzed by analysis of variance and Dunnett's test, $p<0.05$.

Pathology

Interim kills of 5 control rats and 5 rats exposed to asbestos were conducted at the end of the 7-month exposure,

and at 1 and 6 months post-exposure (8 and 13 experimental months). A similar interim kill at 18 months post-exposure (25 months of the study) was conducted on 4 control and 4 exposed rats. (Hamsters were not killed at any of the interim kills because of the limited group size).

At these intervals, the designated rats were starved overnight and killed by decapitation. Immediately prior to sacrifice, the rats' tracheas were clamped under methoxyflurane anesthesia in order to avoid aspiration of blood. The lungs and trachea were removed and subsequently distended with phosphate buffered 10% formalin. The lungs, thoracic lymph nodes and representative portions of heart, kidney, liver, spleen, adrenal, testes, trachea, esophagus, accessory sex glands, stomach, thyroid, parathyroid, aorta, pancreas, small intestines, brain, pituitary, urinary bladder and any other tissues suggestive of a pathologic process were preserved in formalin fixative. Nasal turbinates from rats of the 6 month post exposure (13th month of the study) kill were also preserved in the fixative. Routine procedures were used to prepare paraffin-embedded tissue sections that were subsequently stained with hematoxylin and eosin (H&E). Additional sections of lungs and thoracic lymph nodes from all interim-kill rats were stained with special stains to detect the presence or absence of collagen

(Masson's Trichrome stain) and of reticulin (Gordon and Sweet's, or Gridley's or Gomori's staining procedure). The resultant sections of all rats were examined for histopathologic changes. Special attention was given to the lungs and thoracic lymph nodes to define the response to repeated inhalation of the asbestos dust.

All rats not killed at interim kill dates were maintained under control conditions until they died spontaneously or were killed in a moribund condition (maximum of 870 days after start of exposure). All hamsters were retained under control conditions until they died spontaneously or were killed in a moribund condition (maximum of 723 days after start of exposure). All these animals were subjected to necropsy examination and the lungs were distended with phosphate buffered 10% formalin. The lungs, thoracic lymph nodes, and representative portions of heart, kidney, liver, spleen, adrenal, testes, trachea, esophagus, and any other tissues suggestive of a pathologic process or tumor formation were preserved in formalin fixative. Hematoxylin and eosin stained sections of these tissues were routinely prepared for histopathologic examination.

Thorough gross and histopathologic examination was conducted on tissues of rats and hamsters in order to (a) ascertain the probable cause of death, (b) define possible pulmonary response, and (c) evaluate tumor incidence.

Tumor incidence data were statistically evaluated with Fisher's Exact Probability Test. In all cases, probability values (p) of less than 0.05 were interpreted as indicating significant differences.

RESULTS

Chamber Atmosphere

A typical sample of asbestos dust retained on a membrane filter is shown in the scanning electron micrograph (Fig. 2). The dust consisted mainly of amorphous particulate matter and some fibrous material.

Gravimetric analyses of over 400 samples of asbestos dust indicated that the average dust concentration in the chamber atmosphere was 85 ± 52 milligrams per cubic meter of air. Particle size distribution analyses of the dust samples dispersed in mounting medium revealed an average number-length-mean diameter of 0.8 µm. However, direct measurement of the dust particles suspended in air with a light scattering particle counter showed an average number-length-mean diameter of 4.1 µm. The larger diameter recorded by the light scattering measurement technique suggests agglomeration of dust particles suspended in the chamber atmosphere.

Animal Observation

During each exposure period, signs of slight ocular and nasal irritation were observed in both rats and hamsters. The animals buried their muzzles in the hair coat. The animals remained inactive until they were removed from the

dust atmosphere at the termination of each exposure.

The body weight data (Fig. 3) indicated that after 1 month of exposure to asbestos dust, the mean body weights of rats were significantly lower than those of control rats. Weight gain improved slightly following termination of the exposures, but the mean body weights remained significantly lower than those of the control group until 14 months post exposure (21 experimental months). The mean body weights of the exposed hamsters were statistically decreased from those of the control animals on two occasions during the first month of the experiment. After 3 months of exposure, the test hamster's body weights remained statistically increased compared to controls, except on isolated occasions, until the end of the study.

Mortality data for rats (Fig. 4) indicated no significant difference between exposed and control rats. Ninety percent of the rats died during the observation period between the 7th and 30th experimental months. Forty percent of the hamsters exposed to asbestos dust (Fig. 5), died during the 7 month exposure period. Remaining exposed hamsters died within 10 months post-exposure. Control hamsters did not start dying until 2 months post-exposure and some survived as long as 16 months post-exposure (23 experimental months). Thus, the lifespan of hamsters appeared to be significantly reduced by the exposure regimen used in this study.

Pathology - Rats (See Tables 2 & 3*)

In rats killed at the end of the 7-month exposure, pulmonary deposits of the dust were visible grossly as isolated subpleural pale foci, usually less than 2 mm in diameter. Microscopically, the principal changes were isolated aggregates of dust-laden macrophages within alveoli. Many of the affected alveoli were those that evaginate off the alveolar ducts or repiratory bronchioles of the pulmonary raceme. The alveolar membranes adjacent to these aggregates showed a very slight focal hypercellularity and thickening, but no discernible increase in reticulin or collagen deposition. The pulmonary interstitium and satellite thoracic lymph nodes sometimes contained aggregates of the dust, both extracellular and intracellular within macrophages, with typically no significant increase in reticulin or collagen content.

At subsequent evaluations during the post-exposure period (8, 13 and 25 months of the experiment), pulmonary reaction similar to that described at 7 months was noted. There were no marked accumulations of intraalveolar proteinaceous material, leukocytes or inflammatory debris nor were there marked fibrogenic responses in the lungs.

*Appendixes A-D to this report contain gross and histopathologic observations on control and asbestos-exposed rats dying during the course of the study and also gross and histopathologic observations on non-pulmonary tissues examined at the interim examinations.

During the period from the 14th month to the end of the study at 29 months, the pulmonary response to asbestos also included some cases of focal alveolar hyperplasia, alveolar adenomatous proliferation, non-progressive fibrosis and squamous metaplasia of alveoli. Pulmonary deposits of asbestos dust were no longer grossly visible by this time. More importantly, 6/34* rats exposed to asbestos and examined after months 13 of the study had pulmonary carcinoma formation as compared to 0/35* control rats with pulmonary tumors. The pulmonary carcinomas were seen in rats that died from 16 to 29 months after the initiation of the experiment (294 to 571 days post-exposure).

The incidences of all types of tumors found in control and asbestos exposed rats are summarized in Table 4**. Statistical evaluation using Fisher's Exact Probability test showed that the incidence of pulmonary carcinomas was significantly increased in the group exposed to asbestos. The incidences of non-pulmonary tumors were comparable in both asbestos exposed and control rats.

Histopathologic studies of other, non-pulmonary, tissues revealed no alterations considered related to exposure to the asbestos dust.

* A total of 15 rats per group had been killed for interim examinations at 7, 8 and 13 months of the study and one exposed rat was missing.

**Appendixes E and F contain a listing of the temporal incidence of all tumors in control and asbestos exposed rats respectively.

Pathology - Hamsters*

Hamsters that died during the exposure period had evidence of ulcerative enteritis and/or amyloidosis. Since ulcerative enteritis and amyloidosis can occur spontaneously in hamsters and were, in fact, later found in several control hamsters, it is difficult to consider the exposure to asbestos as the sole factor in this early mortality.

However, it appears as if the exposure to asbestos or the stress of the exposure regimen was at least partially responsible for the earlier mortality observed in these hamsters exposed to asbestos.

Two hamsters died during the exposure period with pulmonary lesions, one with focal consolidation of the lungs and one with pulmonary ectatic emphysema. These isolated cases may or may not have been related to asbestos dust exposure. All other tissue alterations in hamsters were considered spontaneous in nature and unrelated to treatment.

The ability to evaluate long-term pulmonary effects associated with chronic inhalation of the asbestos was severely limited by the early mortality of 8/15 hamsters. The following comments are based on the examination of the remaining

*Appendixes G and H to this report contain mortality data and gross and histopathologic observations on individual control and asbestos-exposted hamsters respectively.

7/15 hamsters that died spontaneously from 10-16 months after initiation of the study.

Deposits of the asbestos dust were not grossly visible in the lungs or thoracic lymph nodes. Microscopically, the principal pulmonary changes in exposed animals were isolated aggregates of particle-laden macrophages within alveoli. The alveolar walls adjacent to these aggregates were slightly thickened. Minimal focal alveolar epithelial hyperplasia near the affected bronchioles of the lung was observed in 3 of the 15 hamsters examined. In the control group of hamsters major pulmonary lesions were as follows: focal alveolar epithelial hyperplasia in 2/15 hamsters; eosinophilic material and pigment-laden macrophages in alveoli of 2/15 hamsters; cholesterol clefts and mineralized deposits in 1/15 hamsters.

Based on the equivocal observations made on this limited number of hamsters, there was no conclusive evidence of a significant pulmonary response to exposure to asbestos dust in this species.

There were two cases of tumor formation in control hamsters, one a malignant lymphoma with widespread metastasis and one an adrenal cortical adenoma. There were no tumors observed in the 15 hamsters exposed to asbestos. This observation must be considered in light of the fact that 6 of the 15

hamsters in the asbestos group died within the initial 7 months of the study, whereas no controls died before the 9th month of the study.

DISCUSSION

The results of the present study indicate that exposure to asbestos pipe-covering dust at an average concentration of 85 mg/M^3, for 6 hours per day, 5 days per week for 7 months caused pulmonary carcinomas in SPF-derived Sprague-Dawley male rats. The earliest pulmonary carcinoma was found in a rat that died 477 days (approximately 16 months) after initiation of exposure. Pulmonary carcinomas were found in ~18% of the rats surviving longer than 13 months.

In studies by Gross et al.[21] (1967), rats which were not SPF derived were exposed to chrysotile fibrous dusts. The average dust concentration was 86 mg/M^3 and the duration of exposure was 62 weeks (approximately 14 months). The incidence of tumors observed in their rats was approximately 16% and the first pulmonary carcinoma was found in a rat that died 16 months after initiation of exposure. In a comparison of the results of the two studies, it is interesting to note that the incidence of tumors in their rats was approximately the same as in our rats even through their animals were exposed for twice as long to a similar concentration. The latent period for tumor development was practically the same (16 months) in both studies.

In similar studies by Reeves et al.[22] (1971), rats were exposed to chrysotile dust at a lower concentration of 48 mg/M^3

for only 4 hours a day, 4 days per week for 99 weeks (approximately 23 months). No pulmonary cancers were found. However, in an identical inhalation study with crocidolite asbestos dust, Reeves et al. noted a low incidence of pulmonary squamous-cell carcinomas.

Two of the factors believed to be associated with carcinogenicity of asbestos are (1) the morphology and (2) the trace metal contents of the material. Morphologically, the asbestos dusts used in the present experiment contained mainly 0.5 to 10.5 μ particles and very few fibers (Fig. 2). Thus, the production of pulmonary carcinoma in the present experiment supports the conclusion of Kogan et al., who considered fiber length or fibrous structure as non-essential for pathogenicity.[23] Regarding the trace metal contents (Table 5), the quantities of nickel, chromium and cobalt in the asbestos sample used in our experiment were quite comparable to those of the UICC (Union Internationale Contre Le Cancer) reference standard sample,[24] but were 2 to 4 times higher than the chrysotile samples of Gross et al.,[21] and Reeves et al.[22] The high content of trace metals in the sample used in the present experiment may be an explanation of its high carcinogenic potency. On the other hand, the success of producing lung cancer with crocidolite[22] which contained rather low concentrations of nickel and cobalt indicates that the

mechanism of pulmonary carcinoma induction by asbestos dusts may not be entirely related to the content of trace metals. Additional studies are needed to elucidate the mechanism of carcinogenesis by asbestos dust. Furthermore, it would be necessary to examine the chronic effects from inhalation exposure to lower dust concentrations to determine a realistic industrial handling guideline based on animal studies.

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TABLE 1

ATOMIC EMISSION SPECTROGRAPHIC ANALYSIS OF ELEMENTS
PRESENT IN THE BALL MILLED ASBESTOS SAMPLE
USED IN INHALATION EXPOSURE OF RATS AND HAMSTERS

Element	Weight % of Sample
Al	8.0
Ba	0.008
B	<0.05
Ca	0.4
Cd	<0.05
Co	0.004
Cu	<0.001
Cr	0.07
Fe	2.0
Mg	11.0
Mn	0.04
Ni	0.09
Pb	0.01
Si	10.0
Sn	<0.01
Sr	<0.001
Na	1.0
K	<2.0
Ti	0.5
V	<0.005
Zn	<0

TABLE 2

GROSS PATHOLOGIC OBSERVATIONS ON PULMONARY TISSUES OF MALE RATS
KILLED AT SERIAL TIME INTERVALS DURING INHALATION STUDY WITH ASBESTOS

Time Interval in Months	7	7	8	8	13	13	25	25
Treatment Group	Control	Asbestos	Control	Asbestos	Control	Asbestos	Control	Asbestos
Number of Rats	5	5	5	5	5	5	4	4
Gross Pulmonary Observations:								
Multiple circumscribed pale subpleural foci, 1-2 mm	0	3	0	1	0	1	0	0
Darkened appearance of lungs	0	1	0	0	0	0	0	0
Focal reddened areas in lungs	4	1	0	0	0	0	0	0
Particles within thoracic lymph nodes	0	0	0	0	0	0	0	2

Data listed as number of rats in each group showing the various observations.

TABLE 3

HISTOPATHOLOGIC OBSERVATIONS ON PULMONARY TISSUES OF MALE RATS
KILLED AT SERIAL TIME INTERVALS DURING INHALATION STUDY WITH ASBESTOS

Time Interval in Months	7	7	8	8	13	13	25	25
Treatment Group	Control	Asbestos	Control	Asbestos	Control	Asbestos	Control	Asbestos
Number of Rats	5	5	5	5	5	5	4	4
Microscopic Pulmonary Observations:								
Alveoli and Alveolar Membrane								
Isolated focal aggregates of particle-laden alveolar macrophages	0	5	0	5	0	5	0	4
Isolated focus of inflammatory cells in lungs	0	0	2	0	1	0	0	0
Isolated aggregates of alveolar macrophages	0	0	3	0	5	0	0	0
Isolated focus of alveolar epithelial hyperplasia	0	0	0	0	0	0	0	2
Isolated focus of hypercellularity of alveolar wall	0	0	3	0	1	2	0	0
Isolated foci of hypercellularity and thickening of alveolar walls adjacent to particle-laden alveolar macrophages - very slight to equivocal	0	5	0	5	0	4	0	4
Very slight to equivocal increase in collagen and reticulin in affected alveolar walls	0	3	0	3	0	0	0	1
Very slight to slight increase in collagen and reticulin in affected alveolar walls	0	0	0	0	0	0	0	3
Pulmonary carcinoma, with both adenomatous and mucinous areas	0	0	0	0	0	0	0	1
Sarcomatous-like proliferation of tissue in lung and thorax	0	0	0	0	0	0	0	1
Pronounced deposition of connective tissue in lung	0	0	0	0	0	0	0	1
Adenomatous proliferation of bronchial epithelium	0	0	0	0	0	0	0	1

Data listed as number of rats in each group showing the various observations.

TABLE 3 (CONTINUED)

HISTOPATHOLOGIC OBSERVATIONS ON PULMONARY TISSUES OF MALE RATS
KILLED AT SERIAL TIME INTERVALS DURING INHALATION STUDY WITH ASBESTOS

Time Interval in Months	7	7	8	8	13	13	25	25
Treatment Group	Control	Asbestos	Control	Asbestos	Control	Asbestos	Control	Asbestos
Number of Rats	5	5	5	5	5	5	4	4
Microscopic Pulmonary Observations:								
Interstitium								
Peribronchiolar, perivascular lymphoid aggregates	0	0	2	0	0	0	3	3
Peribronchiolar lymphoid aggregates containing particle-laden macrophages and particles, with no significant collagen and reticulin	0	1	0	2	0	3	0	1
Thoracic Lymph Nodes								
Intracellular and extracellular deposits of particles, within thoracic lymph nodes	0	2	0	5	0	3	0	2
Submucosal tracheitis, slight	0	0	0	0	1	1	0	0

Data listed as number of rats in each group showing the various observations.

TABLE 4

SUMMARY[a] OF TUMOR INCIDENCE IN GROUPS OF MALE RATS
USED IN INHALATION STUDY WITH ASBESTOS
(Or Used as Controls for the Study)

Group	Control	Asbestos
Number of Rats Examined	50	49[b]
Number of Rats with Tumors	19	20
Number of Tumors	23	34
Mean Number of Tumors/Rats with Tumors	1.2	1.7
Lung		
Papillary adenocarcinoma	0/50	3/49
Epidermoid carcinoma	0/50	2/49
Adenomatous and mucinous carcinoma	0/50	1/49
Total Pulmonary Tumors	0/50 (0/35)	6/49* (6/34)[c]
Pituitary Gland		
Adenoma	6/50	6/49
Adrenal Gland		
Pheochromocytoma	4/50	6/49
Subcutaneous		
Neurofibroma	0/50	1/49
Carcinoma	0/50	1/49
Fibroma	3/50	1/49
Fibroadenoma	1/50	0/49
Pancreas		
Adenoma	2/50	1/49
Islet cell adenoma	1/50	2/49

[a]A record of observations on individual rats is contained in Appendixes A and B.

[b]One rat was missing.

[c]Fifteen of the 49 rats were killed for interim examinations by the 13th month bringing the actual incidence of pulmonary tumors up to 6 of 34.

*Significantly increased as compared to controls when analyzed by Fisher's Exact Probability Test, $p<0.05$.

TABLE 4 (Continued)

SUMMARY OF TUMOR INCIDENCE IN GROUPS OF MALE RATS
USED IN INHALATION STUDY WITH ASBESTOS
(Or Used as Controls for the Study)

Group	Control	Asbestos
Number of Rats Examined	50	49[b]
Number of Rats with Tumors	19	20
Number of Tumors	23	34
Mean Number of Tumors/Rats with Tumors	1.2	1.7
Brain		
Craniopharyngioma	1/50	0/49
Heart		
Rhabdomyosarcoma	1/50	0/49
Thyroid		
Adenoma	2/50	6/49
Zymball Gland		
Carcinoma	1/50	0/49
Small Intestine		
Mucinous adenocarcinoma	0/50	1/49
Testes		
Interstitial cell tumor	0/50	1/49
Intraabdominal		
Malignant schwannoma	0/50	1/49
Unclassified sarcoma	1/50	1/49

[a]A record of observations on individual rats is contained in Appendixes A and B.

[b]One rat was missing.

[c]Fifteen of the 49 rats were killed for interim examinations by the 13th month bringing the actual incidence of pulmonary tumors up to 6 or 34.

*Significantly increased as compared to controls when analyzed by Fisher's Exact Probability Test, $p<0.05$.

TABLE 5

NICKEL, CHROMIUM AND COBALT
CONTENTS OF ASBESTOS SAMPLES

Elements	Asbestos Pipe Covering Dust*	Reference Samples			
		Gross et al[21] Chrysotile	Reeves et al[22] Chrysotile	Reeves et al[22] Crocidolite	UICC[24] Reference
	%	%	%	%	%
Nickel	0.09	0.0245	0.037-0.046	0.009-0.011	0.079-0.099
Chromium	0.07	0.0153	0.038-0.042	---	0.032-0.049
Cobalt	0.004	0.0022	0.0038-0.0041	0.0012	0.0045-0.0046

*From results of atomic emission spectrographic analysis of ball milled asbestos sample used in this study.

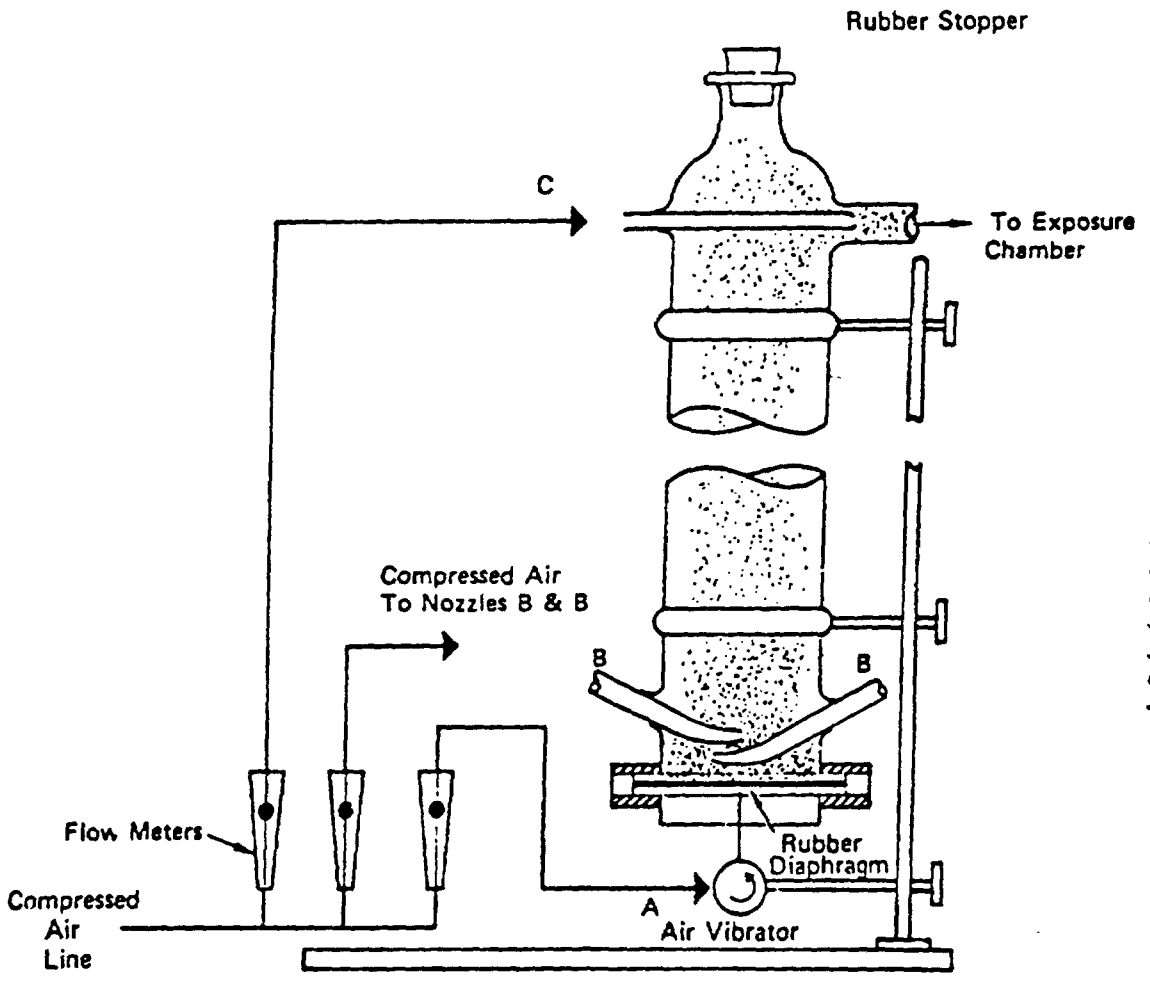


Fig. 1. A schematic diagram of the air elutriator dust generator. Compressed air passes flow meters to an air vibrator (A) and two air nozzles (B) to stir up the dust. Air ejected from nozzle (C) blows the dust over to exposure chamber.

Fig. 2. Scanning electron micrograph of asbestos dusts retained on filter 2470x (2.5 cm=10μ)

Figure 3
MEAN BODY WEIGHTS OF MALE RATS AND HAMSTERS EXPOSED TO ASBESTOS DUSTS OR MAINTAINED AS CONTROLS

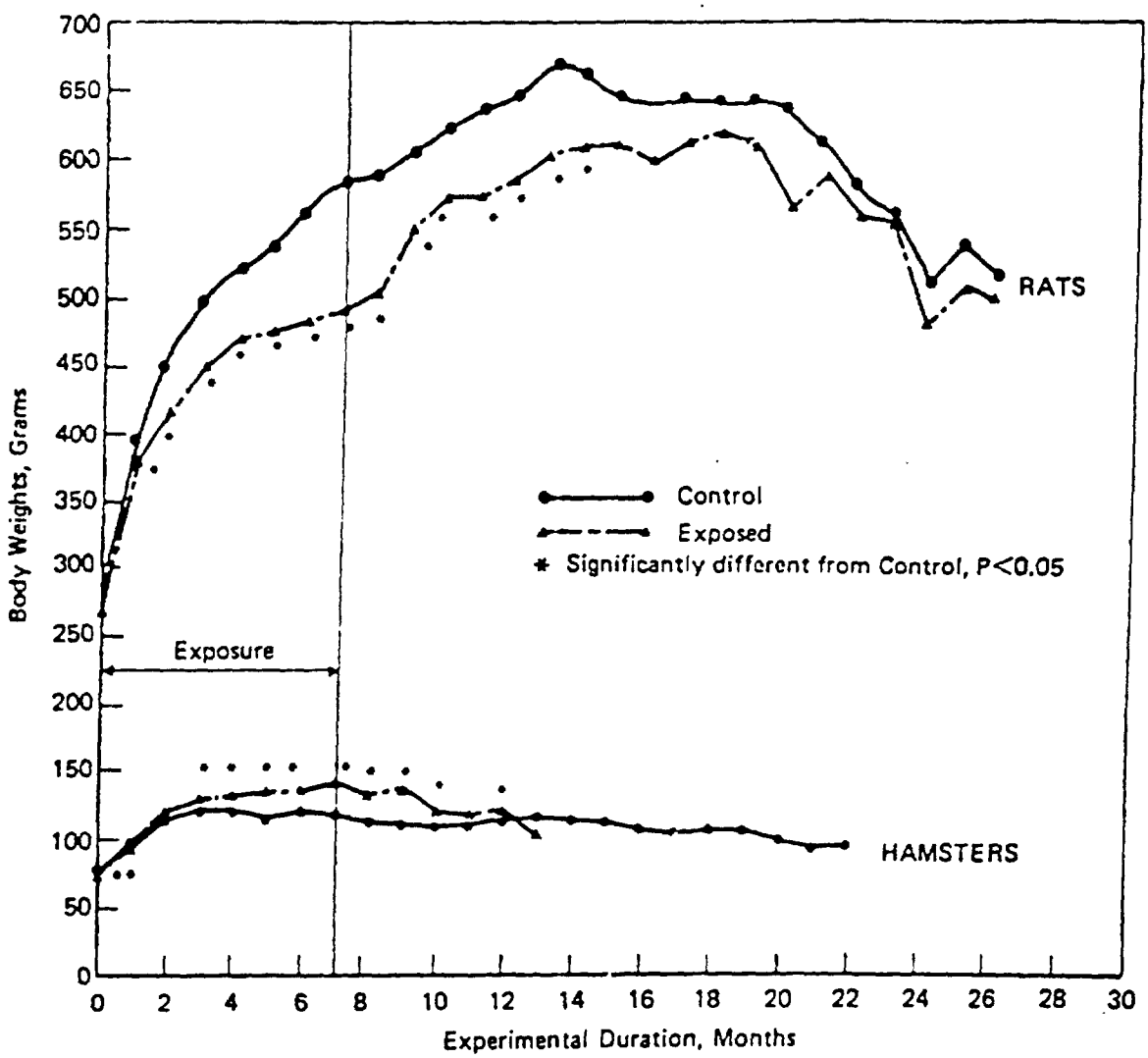
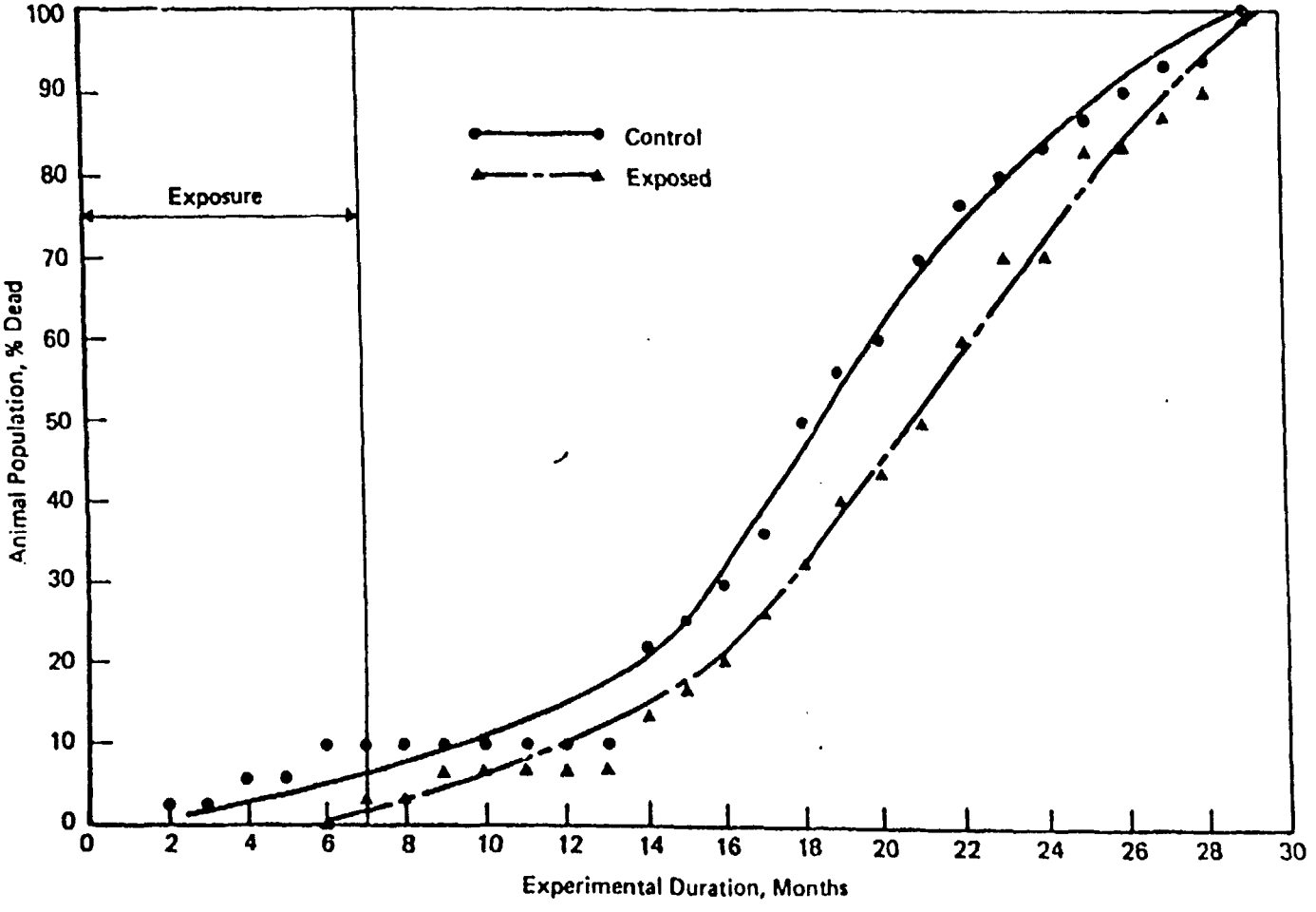


Figure 4
CUMULATIVE PERCENT MORTAILITY OF MALE RATS EXPOSED TO ASBESTOS DUSTS AND THOSE MAINTAINED AS CONTROLS



APPENDIX A

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING MAINTAINED AS CONTROLS FOR INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at time of Death	Gross and Microscopic Observations
72-105	60	Gross: Killed; moribund, due to traumatic injury to upper incisors and overgrowth of lower incisors; decreased adipose tissue. Microscopic: Odontitis, peridontitis and gingivitis secondary to trauma; focal interstitial pneumonitis; focal hepatocellular degeneration and inflammation.
72-146	109	Gross: Killed; cyst in the region of the brain and pituitary, 1 cm in diameter. Microscopic: Proliferating cystic structure in region of ventral aspect of brain and pituitary (craniopharyngioma).
72-134	186	Gross: Killed; large subcutaneous nodular structure weighing 169.5 grams, consisting of semi-gelatinous tissue with non-fibrous areas; generalized anemia. Microscopic: Subcutaneous fibroma; increased splenic hemopoiesis; increased hemopoiesis in liver.
72-115	409	Gross: Killed; large subcutaneous mass weighing 134.5 grams; heart dilated. Microscopic: Subcutaneous fibroma; slight chronic nephropathy; myocardial degeneration; intestinal nematodiasis.
72-131	409	Gross: Killed; excessive adipose tissue; edema of testes and scrotal region. Microscopic: Vacuolation of adrenal cortical cells; pituitary adenoma; focal pancreatic atrophy and fibrosis; hyperplasia of pancreatic islet; slight chronic nephropathy; isolated focus of inflammatory cells in lung.

APPENDIX A (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING MAINTAINED AS CONTROLS FOR INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at time of Death	Gross and Microscopic Observations
72-148	413	Gross: Killed; moribund; over 130 ml of serosanguineous fluid in abdomen; highly lobulated dense white mass incorporating stomach, small and large intestines, and mesentery; metastatic transplantations on the diaphragm and peritoneal cavity. Microscopic: Intraabdominal sarcoma, with extension via abdominal region; moderate chronic nephropathy; increased splenic hemopoiesis; scattering of alveolar macrophages in lungs.
72-149	420	Gross: Died; advanced autolysis; multiple nodular areas in the pancreas 1 mm to ½ cm in diameter; enlarged kidneys with multiple pale foci on the cortex and dilated renal pelvis; pale circumscribed area on liver; enlarged parathyroid glands. Microscopic: Pancreatic adenoma; pronounced chronic nephropathy; pituitary cyst formation; isolated aggregates of particle-laden macrophages in lung; periarteritis; testicular atrophy; skeletal muscle degeneration; increased splenic hemopoiesis; myocardial degeneration; hepatocellular hyperplastic nodule.
72-139	423	Gross: Killed; enlarged lobes of prostate containing green-yellow exudate. Microscopic: Moderate chronic nephropathy; myocardial degeneration; degeneration of myocardial vessels; intestinal nematodiasis; increased splenic hemopoiesis; increased reticuloendothelial proliferation in spleen; hepatic lipidosis; diffuse suppurative inflammation adjacent to urinary bladder and sex glands.

APPENDIX A (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING MAINTAINED AS CONTROLS FOR INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at time of Death	Gross and Microscopic Observations
72-108	456	Gross: Died; advanced autolysis; enlarged, pitted, and mottled surface appearance of kidneys: gastrointestinal contents consisting of dark black material, suggestive of uremia. Microscopic: Pronounced chronic nephropathy with mineralization; secondary parathyroid hyperplasia; myocardial degeneration with mineralization; aortic mineralization.
72-137	485	Gross: Died; slight autolysis; mass in left atrium and ventricle. Microscopic: Proliferating neoplastic mass along endocardial aspect of heart, tentatively diagnosed as cardiac rhabdomyosarcoma; atrial thrombosis; increased splenic hemopoiesis; pulmonary exfoliation of heart failure type cells; metastasis of tumor to thoracic lymph nodes.
72-106	504	Gross: Died; depleted adipose tissue; enlarged, dilated kidneys; aorta dilated; darkening of lungs possibly post-mortem; testes decreased in size. Microscopic: Pronounced chronic nephropathy with mineralization; myocardial degeneration with mineralization; degeneration of myocardial vessels; testicular atrophy; aortic mineralization; lung mineralization.

APPENDIX A (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING MAINTAINED AS CONTROLS FOR INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at time of Death	Gross and Microscopic Observations
72-109	513	Gross: Killed; overgrown incisors and necrotic area of hard palate; pale, pitted kidneys with numerous cystic spaces. Microscopic: Moderate chronic nephropathy; degeneration of myocardial vessels; increased splenic hemopoiesis; secondary parathyroid hyperplasia; periarteritis; peribronchiolar lymphoid aggregates; one focus of alveolar fibrosis and cholesterol cleft formation.
72-113	529	Gross: Died; moderate autolysis; mottled surface of kidneys. Microscopic: Pronounced chronic nephropathy; hepatic congestion; increased splenic hemopoiesis; myocardial degeneration; vacuolation of adrenal cortical cells; periarteritis, dystrophic mineralized focus in lung.
72-111	536	Gross: Died; subcutaneous nodule weighing 7.4 gm, 2 cm in diameter; lungs appear darkened; enlarged kidneys with mottled surface appearance. Microscopic: Pronounced chronic nephropathy; myocardial degeneration; degeneration of myocardial blood vessels; increased splenic hemopoiesis; hepatic congestion; subcutaneous fibroadenoma.

APPENDIX A (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING MAINTAINED AS CONTROLS FOR INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at time of Death	Gross and Microscopic Observations
72-112	543	Gross: Died; moderate autolysis; overgrown incisor; enlarged kidneys, mottled surface appearance; dilated renal pelvis. Microscopic: Pronounced chronic nephropathy with cyst formation; hepatic foci of inflammatory cells; increased splenic hemopoiesis, increased pigment in spleen; degeneration of myocardial vessels; vacuolation of adrenal cortical cells; aortic mineralization.
72-118	547	Gross: Killed; moribund; corneal opacity; subcutaneous nonfibrous mass adjacent to ear canal. Microscopic: Zymbal gland carcinoma; moderate chronic nephropathy; increased pigment in spleen; vacuolation of adrenal cortical cells.
72-120	556	Gross: Died; moderate autolysis; enlarged pituitary; excessive mammary development. Microscopic: Pituitary adenoma; pronounced chronic nephropathy with mineralization; myocardial degeneration; degeneration of myocardial vessels; aortic mineralization; isolated foci of inflammatory cells in lungs; subcutaneous galactocele.
72-121	556	Gross: Died; kidneys pitted and roughened; inelastic aorta; nodular areas in pancreas. Microscopic: Moderate chronic nephropathy; myocardial degeneration; aortic mineralization; no change in pancreatic tissue examined.

APPENDIX A (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING MAINTAINED AS CONTROLS FOR INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at time of Death	Gross and Microscopic Observations
72-123	604	Gross: Killed; large subcutaneous mass 7x7x4 cm weighing 109 grams; kidneys slightly pitted. Microscopic: Subcutaneous fibroma; pronounced chronic nephropathy.
72-125	618	Gross: Killed; moriburd; enlarged, pitted, mottled surface of kidneys with multiple cysts; enlarged parathyroid glands; multiple reddened and golden brown areas of the lungs; demineralization of the bones; Microscopic: No microscopic examination conducted on tissues.
72-127	631	Gross: Died; advanced autolysis; enlarged parathyroids; enlarged, pale, pitted kidneys with mottled surface; hydrothorax; lungs edematous; aorta and aortic arch had loss of elasticity; heart dilated; testes decreased in size and flaccid. Microscopic: Pronounced chronic nephropathy with mineralization; myocardial degeneration with mineralization; degeneration and mineralization of myocardial vessels; thyroid adenoma; periarteritis; aortic mineralization; exfoliation of heart failure cells within alveoli of lung; mineralization of lungs.

APPENDIX A (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING MAINTAINED AS CONTROLS FOR INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at time of Death	Gross and Microscopic Observations
72-129	634	Gross: Died; left corneal opacity; enlarged, pale, mottled surface of kidneys with cystic structures; decreased adipose tissue; aorta distended with loss of elasticity; testes decreased in size and flaccid; stomach contained red material; mesenteric lymph nodes tortuous and nodular. Microscopic: Pronounced chronic nephropathy; myocardial degeneration and inflammation; periarteritis; testicular atrophy; adrenal cortical hyperplastic nodule; vacuolation of adrenal cortical cells; secondary parathyroid hyperplasia; increased reticulo endothelial proliferation in spleen; peribronchiolar lymphoid aggregates; edema of lymph nodes; aortic mineralization.
72-128	641	Gross: Died; slight autolysis; darkening of lungs; enlarged pituitary (assumed pituitary adenoma). Microscopic: Moderate chronic nephropathy; myocardial degeneration; postmortem congestion of lungs; pituitary unavailable for examination.
72-132	652	Gross: Killed; moribund; bilateral, partial corneal opacity; mottled surface appearance of lungs; enlarged, pitted, mottled kidneys with cystic structures; mesenteric aneurysm; testes decreased in size and flaccid; anemic appearance of tissues. Microscopic: Pronounced chronic nephropathy; increased splenic hemopoiesis; vacuolation of adrenal cortical cells; periarteritis; myocardial degeneration; aortic mineralization; increased alveolar macrophages; proteinaceous material and fibrosis of alveolar walls; thoracic lymph nodes edematous; testicular atrophy.

APPENDIX A (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING MAINTAINED AS CONTROLS FOR INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at time of Death	Gross and Microscopic Observations
72-133	665	Gross: Died; moderate autolysis; enlarged prostate; mesenteric vessels dilated; pitted, cystic cortex of kidneys; enlarged parathyroids; gastric mucosa mineralization; testes decreased in size and flaccid. Microscopic: Periarteritis with thrombosis; pronounced chronic nephropathy; testicular atrophy, myocardial degeneration; secondary parathyroid hyperplasia; vacuolation of adrenal cortical cells; suppurative prostatitis; increased alveolar macrophages (heart failure cells) in lung.
72-135	697	Gross: Killed; moribund; enlarged pituitary with a darkened area (adenoma); mottled surface of kidneys; two nodular structures in mesentery (4-5 mm) (6-7 mm); a focal reddened area in one adrenal gland. Microscopic: Moderate chronic nephropathy; increased splenic hemopoiesis; increased pigment in spleen; myocardial degeneration; adrenal cortical hyperplastic nodule; adrenal hematocyst; edematous mesenteric lymph nodes; pituitary unavailable for examination.
72-136	728	Gross: Died; enlarged, pale, mottled surface of kidneys; enlarged parathyroids; bones soft and friable; large vessels of thoracic and abdominal region dilated with loss of elasticity; atrial thrombosis. Microscopic: Pronounced chronic nephropathy; myocardial degeneration; degeneration of myocardial vessels; increased splenic hemopoiesis; periarteritis; testicular atrophy; aortic mineralization; atrial thrombosis; increased alveolar macrophages within alveoli and focal fibrosis of alveoli.

APPENDIX A (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING MAINTAINED AS CONTROLS FOR INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at time of Death	Gross and Microscopic Observations
72-143	739	Gross: Killed; moribund; emaciated; 25-30 ml serosanguineous fluid in peritoneal cavity; enlarged, pale kidneys with cystic structures; multiple coalescing pale foci in liver; tough focal capsular areas on liver; nodular structures throughout pancreas; cystic structure between liver and stomach, 5 cm in diameter; several focal pale areas in ventricles; aorta distended with loss of elasticity; enlarged parathyroid glands; thoracic lymph nodes green-brown in color. Microscopic: Pronounced chronic nephropathy with cyst formation; focal hepatic lipoidosis; periarteritis: testicular atrophy; aortic mineralization; myocardial degeneration and inflammation; secondary parathyroid hyperplasia; adrenal pheochromocytoma; hepatic cyst; pancreatic adenoma.
72-145	756	Gross: Died; advanced autolysis; enlarged, mottled surfaces of kidneys; enlarged parathyroid glands. Microscopic: Pronounced chronic nephropathy; myocardial degeneration; degeneration of myocardial vessels; secondary parathyroid hyperplasia; testicular atrophy; periarteritis; aortic mineralization; intra-alveolar aggregates of exfoliated alveolar macrophages (heart failure cells).

APPENDIX A (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING MAINTAINED AS CONTROLS FOR INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

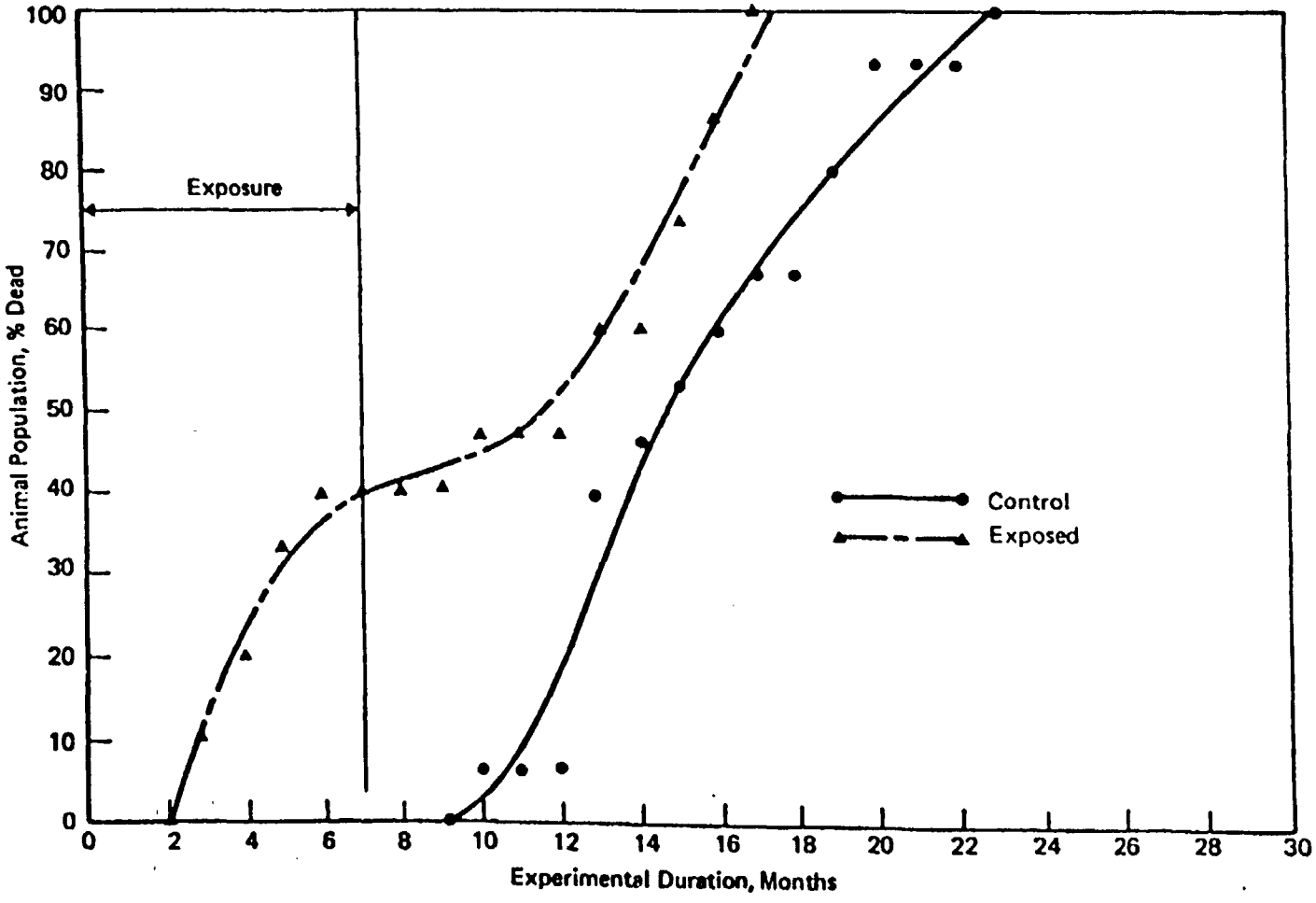
Pathology Number	Days on Test at time of Death	Gross and Microscopic Observations
72-104	870	Gross: Killed; corneal opacity; enlarged parathyroid glands; enlarged, mottled surface of kidneys; enlarged right adrenal (10-15 x normal), dark and hemorrhagic in color; two nodular structures in pancreas; mesenteric vessels tortuous and sclerotic; testes decreased in size and flaccid; liver had focal pale areas; multiple subpleural circumscribed reddened foci in lungs; loss of elasticity of aorta. Microscopic: Pronounced chronic nephropathy; pituitary adenoma; adrenal pheochromocytoma; pancreatic islet cell adenoma; pigmentation and edema of lymph nodes; myocardial degeneration and inflammation of degeneration of myocardial vessels; increased pigment in spleen; aortic mineralization; keratitis; periarteritis; testicular atrophy; decreased secretory content of accessory sex glands; increased number of reticuloendothelial cells in liver; subpleural aggregates of alveolar macrophages containing hematogenous pigment.

APPENDIX A (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING MAINTAINED AS CONTROLS FOR INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at time of Death	Gross and Microscopic Observations
72-150	806	Gross: Killed; moribund; emaciated; testes decreased in size and flaccid; decreased adipose tissue; mesenteric lymph nodes darkened; enlarged left adrenal; enlarged, pale, mottled kidneys with cystic structures; mineralization of gastric mucosa; liver pale with subcapsular pale foci; bones demineralized; aorta overdistended with loss of elasticity; enlarged parathyroids; hydrothorax; heart distended and pale; left atrial thrombosis. Microscopic: Pronounced chronic nephropathy with cyst formation; thickening of gastric mucosa with distended gastric pits; pulmonary exfoliation of alveolar macrophages; focal fibrosis and edema of lymph nodes; degeneration of myocardial vessels; myocardial degeneration; atrial thrombosis; diffuse keratitis; aortic mineralization; secondary parathyroid hyperplasia; increased splenic hemopoiesis; vacuolation of adrenal cortical cells; focal pancreatic fibrosis; bilateral adrenal pheochromocytoma; periarteritis; testicular atrophy; decreased secretory content of sex glands; pancreatic islet cell adenoma; increased size of pancreatic islet hepatic cyst formation, diffuse hepatocellular cytoplasmic vacuolation, lipidosis, bile duct hyperplasia, focal necrosis and inflammation and microcyst formation.

Figure 5
CUMULATIVE PERCENT MORTAILITY OF MALE HAMSTERS EXPOSED TO ASBESTOS DUSTS AND THOSE MAINTAINED AS CONTROLS



APPENDIX A (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING MAINTAINED AS CONTROLS FOR INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at time of Death	Gross and Microscopic Observations
72-104	870	Gross: Killed; corneal opacity; enlarged parathyroid glands; enlarged, mottled surface of kidneys; enlarged right adrenal (10-15 x normal), dark and hemorrhagic in color; two nodular structures in pancreas; mesenteric vessels tortuous and sclerotic; testes decreased in size and flaccid; liver had focal pale areas; multiple subpleural circumscribed reddened foci in lungs; loss of elasticity of aorta.
		Microscopic: Pronounced chronic nephropathy; pituitary adenoma; adrenal pheochromocytoma; pancreatic islet cell adenoma; pigmentation and edema of lymph nodes; myocardial degeneration and inflammation of degeneration of myocardial vessels; increased pigment in spleen; aortic mineralization; keratitis; periarteritis; testicular atrophy; decreased secretory content of accessory sex glands; increased number of reticuloendothelial cells in liver; subpleural aggregates of alveolar macrophages containing hematogenous pigment.

APPENDIX B

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING USED IN INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at Time of Death	Gross and Microscopic Observations
72-198	200	Gross: Killed; moribund due to traumatic injury to lower incisor teeth and resultant hemorrhage; focal white areas in lungs, suggestive of aggregates of alveolar macrophages.
		Microscopic: Lungs contained aggregates of dust particles, sometimes within cytoplasm of alveolar macrophages; adajcent alveolar walls showing minimal hypercellularity; aggregates of dust particles in thoracic lymph nodes; slight chronic nephropathy.
72-180	260	Gross: Died; advanced autolysis; increased fluidity of intestinal contents; focal white areas in lungs suggestive of aggregates of macrophages.
		Microscopic: Pulmonary aggregates of particle-laden macrophages; aortic mineralization; pronounced chronic nephropathy; myocardial degeneration; testicular atrophy; decreased content of accessory sex glands.
72-154	409	Gross: Killed; Subcutaneous cyst formation within perineal area.
		Microscopic: Subcutaneous cyst formation and granulomatous reaction; slight chronic nephropathy; myocardial degeneration; isolated foci of hypercellularity and thickening of alveolar cells adjacent to aggregates of dust particles, frequently within alveolar macrophages of the lungs; equivocal to very slight increase in fibrogenic tissues within thickened alveoli; pulmonary interstium and thoracic lymph nodes containing aggregates of dust particles, but not accompanied by any fibrogenic response.

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING USED IN INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at Time of Death	Gross and Microscopic Observations
72-152	431	Gross: Killed; corneal opacity; overgrown incisors; isolated subpleural circumscribed white foci in the lungs, 1 mm in diameter, which disappeared upon inflation with formalin; mesenteric tissue thickened in one area, 3 cm in diameter. Microscopic: pulmonary reaction similar to 72-154; focal aggregates of inflammatory cells in liver; increased splenic hemopoiesis; slight chronic nephropathy; mesenteric fat necrosis and inflammation; pituitary microcyst formation; vacuolation of adrenal cortical cells; diffuse keratitis.
72-169	477	Gross: Killed; moribund; enlarged, mottled kidneys with cystic structures; testes decreased in size; mesenteric vessels dilated and sclerotic; diffuse darkened areas in lungs, one of which appeared firm and nodular upon palpation; thoracic lymph nodes enlarged and darkened. Microscopic: pronounced chronic nephropathy; myocardial degeneration; degeneration of myocardial vessels; hepatic lipidosis; periarteritis, testicular atrophy; increased splenic hemopoiesis; secondary parathyroid hyperplasia; adrenal pheochromocytoma; vacuolation of adrenal cortical cells; aortic mineralization; pulmonary papillary adenocarcinoma; pulmonary exfoliation of alveolar macrophages (heart failure cells) plus edema, hemorrhage and reaction as described for 72-154.
72-168	505	Gross: Died; autolysis present; traumatically induced hemorrhage of external nares and nasal turbinates; nasal turbinates hemorrhagic in appearance. Microscopic: increased pigment in spleen; slight chronic nephropathy; myocardial degeneration; degeneration of myocardial vessels; occlusive hemorrhagic rhinitis; same pulmonary reaction as 72-154.

APPENDIX B (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING USED IN INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at Time of Death	Gross and Microscopic Observations
72-158	507	Gross: Killed; enlarged, pitted kidneys with enlarged pelvic portions. Microscopic: Prounounced chronic nephropathy; pulmonary reaction similar to 72-154; aortic mineralization; increased pigment in spleen; myocardial degeneration; degeneration of myocardial vessels; secondary parathyroid hyperplasia; vacuolation of adrenal cortical cells; periarteritis.
72-153	529	Gross: Died; moderate autolysis; kidneys roughened on surface. Microscopic: Pronounced chronic nephropathy; secondary parathyroid hyperplasia; cystic retention of material within thyroid; myocardial degeneration; periarteritis, aortic mineralization; pulmonary reaction like 72-154.
72-155	532	Gross: Died; advanced autolysis; fluidity of contents of distal intestinal tract, dark red in color; pale, pitted kidneys, with mottled surface appearance. Microscopic: Pronounced chronic nephropathy; myocardial degeneration; degeneration of myocardial vessels; periarteritis, testicular atrophy; pulmonary reaction similar to but less than 72-154.

APPENDIX B (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING USED IN INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at Time of Death	Gross and Microscopic Observations
72-157	554	Gross: Died; advanced autolysis; hydrothorax; lungs filled with fluid. Microscopic: Pronounced chronic nephropathy; myocardial degeneration; degeneration of myocardial vessels; periarteritis; vacuolation of cortical cells; focal hepatic fibrosis; epidermoid carcinoma of lung with metastasis to thoracic lymph node; also pulmonary reaction like 72-164 plus exfoliation of macrophages (heart failure cells).
72-160	581	Gross: Died; moderate autolysis; one subpleural circumscribed pale foci in lung; enlarged, pale kidneys Microscopic: Pronounced chronic nephropathy; myocardial degeneration; vacuolation of cortical cells; pulmonary reaction similar to 72-154.
72-162	603	Gross: Killed; moribund; darkened areas in lungs firm on palpation; thoracic lymph nodes containing red pigment; kidneys pitted with mottled surface appearance and cystic areas; enlarged parathyroids; aortic arch dilated and inelastic. Microscopic: Pulmonary reaction similar to 72-154 plus focal alveolar hyperplasia and fibrosis; pronounced chronic nephropathy; increased splenic hemopoiesis; secondary parathyroid hyperplasia; periarteritis; testicular atrophy; aortic mineralization; vacuolation of cortical cells.

APPENDIX B (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING USED IN INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at Time of Death	Gross and Microscopic Observations
72-163	625	Gross: Died; hydrothorax; several subpleural circumscribed pale foci up to 4 mm in lungs; kidneys roughened over surface. Microscopic: Pulmonary epidermoid carcinoma; also reaction similar to but more pronounced than 72-154; aortic mineralization, myocardial degeneration; degeneration of myocardial vessels; secondary parathyroid hyperplasia; pronounced chronic nephropathy; periarteritis.
72-165	630	Gross: Died; enlarged, pitted kidneys; enlarged sublumbar lymph nodes. Microscopic: Pulmonary alveolar adenomatous proliferation; also pulmonary reaction described for 72-154; pronounced chronic nephropathy; myocardial degeneration; vacuolation of cortical cells; edema and pigment within lymph nodes; secondary parathyroid hyperplasia.
72-167	652	Gross: Killed; two subcutaneous masses weighing 64.7 grams and 36.3 grams; pitted kidneys with mottled surface appearance. Microscopic: Subcutaneous neurofibroma; hyperplasia of adrenal medullary cells; pronounced chronic nephropathy; focal inflammation in portal triads and lobules of liver; pulmonary reaction similar to 72-154 plus more lung fibrosis and focus of alveolar adenomatous proliferation.

APPENDIX B (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING USED IN INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at Time of Death	Gross and Microscopic Observations
72-170	652	Gross: Died; emaciated; enlarged parathyroids; enlarged parathyroids; enlarged, pale kidneys with mottled surface and cystic spaces; gastrointestinal tract darkened; gastric wall thickened; aorta dilated and inelastic; no adipose tissue; testes decreased in size.
		Microscopic: Lung reaction like 72-154 plus focal fibrosis and alveolar hyperplasia; aortic mineralization; secondary parathyroid hyperplasia; myocardial degeneration and fibrosis; pronounced chronic nephropathy; periarteritis.
72-171	658	Gross: Died; enlarged kidneys with cysts and mottled surface; enlarged parathyroid; enlarged pituitary dark in appearance; turbinates congested or hemorrhagic.
		Microscopic: Focal pulmonary lung fibrosis and alveolar hyperplasia: also reaction like 72-154; pronounced chronic nephropathy; hepatic portal inflammation; myocardial degeneration; pituitary adenoma; parathyroid not examined.

APPENDIX B (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING USED IN INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at Time of Death	Gross and Microscopic Observations
72-172	661	Gross: Killed; two subpleural circumscribed gray-white foci in lungs 3 mm in diameter; nodular structure in duodenal wall; two nodules in mesentery 1/2 cm and 2/3 cm in diameter; thoracic lymph nodes enlarged; pale kidneys. Microscopic: Pulmonary reaction like 72-154 plus focal alveolar fibrosis and hyperplasia; aortic mineralization; edema of lymph nodes; moderate chronic nephropathy; myocardial degeneration; increased splenic hemopoiesis; periarteritis; secondary parathyroid hyperplasia; adrenal pheochromocytoma; mucinous adenocarcinoma of small intestine; thyroid adenoma.
72-175	675	Gross: Died; moderate autolysis; enlarged, pale, mottled kidneys; enlarged parathyroids; mesenteric blood vessels dilated; left atrial thrombosis; pulmonary consolidation; testes decreased in size. Microscopic: Pronounced chronic nephropathy; myocardial degeneration; vacuolation of cortical cells; adrenal hematocyst; periarteritis; left atrial thrombosis; secondary parathyroid hyperplasia; aortic mineralization; pulmonary reaction like 72-164 plus exfoliation of alveolar macrophages.

APPENDIX E (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING USED IN INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at Time of Death	Gross and Microscopic Observations
72-179	697	Gross: Killed; moribund; multi-loculated hemorrhagic mass within mesentery, 10 cm in diameter; firm nodular structure in pancreatic area of mesentery; enlarged pale spleen; liver pale; aorta with loss of elasticity. Microscopic: Intraabdominal malignant schwannoma; aortic mineralization; pulmonary reaction similar to but less than 72-164; increased splenic hemopoiesis; slight chronic nephropathy; myocardial degeneration; focal aggregates of reticuloendothelial cells in liver; pancreatic islet cell adenoma.
72-190	697	Gross: Died; subcutaneous multi-nodular structure weighing 21 grams; hydrothorax; heart distended and containing blood clots; focal darkened area in lung, 5-7 mm in diameter; enlarged kidneys; enlarged left adrenal; aorta dilated with loss of elasticity; mesenteric vessels tortuous and sclerotic. Microscopic: Lung reaction includes that described for 72-154 plus alveolar hyperplasia, squamous metaplasia and fibrosis; aortic mineralization; pronounced chronic nephropathy; periarteritis; myocardial degeneration; degeneration of myocardial vessels; focal hepatic portal fibrosis; subcutaneous fibroma; adrenal pheochromocytoma; secondary parathyroid hyperplasia; edema and congestion of lymph nodes.

APPENDIX B (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING USED IN INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at Time of Death	Gross and Microscopic Observations
72-181	721	Gross: Died; moderate autolysis; absence of adipose tissue; fluidity of intestinal tract content; mineralization of gastric mucosa; enlarged, pale kidneys with mottled surface appearance; one cyst 3 mm in diameter; liver pale; enlarged parathyroids; nodular structure in pancreas 1/2 cm in diameter. Microscopic: Lung reaction like 72-154 plus focal area of alveolar epithelial adenomatous proliferation; aortic mineralization; pronounced chronic nephropathy; focal hepatocellular vacuolation and lipidosis; focal portal fibrosis in liver; myocardial degeneration; degeneration of myocardial vessels; periarteritis; testicular atrophy; vacuolation of cortical cells; secondary parathyroid hyperplasia; pancreatic adenoma.
72-183	721	Gross: Died; emaciated; advanced autolysis; fluidity of intestinal tract; mineralization of gastric mucosa; enlarged, pale, mottled kidneys with cystic areas. Microscopic: Pronounced chronic nephropathy; periarteritis; testicular atrophy; myocardial degeneration; aggregates of reticuloendothelial cells in liver; increased splenic hemopoiesis; secondary parathyroid hyperplasia; adrenal pheochromocytoma; aortic mineralization; pulmonary reaction similar to 72-154.

APPENDIX B (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING USED IN INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at Time of Death	Gross and Microscopic Observations
72-185	724	Gross: Killed; moribund; scattered subpleural circumscribed pale foci in lungs up to 2 mm in diameter; aorta dilated with loss of elasticity; enlarged parathyroids; liver pale with multiple foci up to 2 mm in diameter on all lobes; uremic gastritis; enlarged, pitted, pale kidneys with multiple cystic structures; decreased adipose tissue; testes decreased in size and flaccid. MMicroscopic: Pulmonary reaction like 72-154 plus more exfoliated macrophages; pronounced chronic nephropathy; focal reticuloendothelial cell aggregates and lipidosis in liver, increased splenic hemopoiesis; myocardial degeneration; degeneration of myocardial vessels; pancreatic islet cell adenoma.
72-195	732	Gross: Killed; moribund; circumscribed area 2 cm in diameter having the consistency of an epidermal inclusion cyst; mesenteric vessels containing multiple nodular areas; fluid in abdominal cavity; enlarged, pale kidneys with multiple cystic areas; right kidney containing a pale circumscribed mass 1 cm above the surface and 1 1/2-2 cm in diameter; fluidity of contents of intestinal tract and stomach; subpleural pale areas in the liver; enlarged, pale parathyroids; hydrothorax; focal reddened area in pituitary; left atrial thrombosis; thoracic lymph nodes enlarged and red-brown in color; two subpleural circumscribed pale foci 1/2 cm in diameter. Microscopic: Pulmonary reaction similar to 72-154, plus increased exfoliated alveolar macrophages and focal alveolar fibrosis; aortic mineralization; adrenal hematocyst and vacuolation of cortical cells; periarteritis and thrombosis; pronounced chronic nephropathy with cyst formations and fetalization of epithelium lining tubules; testicular atrophy; hepatic lipidosis and extramedullary hemopoiesis; granulomatous colitis; secondary parathyroid hyperplasia; myocardial degeneration; atrial thrombosis; pituitary adenoma.

APPENDIX B (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING USED IN INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at Time of Death	Gross and Microscopic Observations
72-200	732	Gross: Killed; moribund; enlargen, hemorrhagic pituitary; enlarged, pale prostate, with purulent material; enlarged, pale kidneys; enlarged parathyroids. Microscopic: Pituitary adenoma; aortic mineralization; vacuolation of adrenal cortical cells; periarteritis; secondary parathyroid hyperplasia; myocardial degeneration and fibrosis; moderate chronic nephropathy with mineralization; focal biliary hyperplasia in liver; increased splenic hemopoiesis; pulmonary reaction like 72-154; prostate not examined.
72-192	812	Gross: Died; enlarged, dark kidneys with scattered pale foci; enlarged liver; 2 subpleural circumscribed gray foci in lungs; pinpoint in size. Microscopic: Pituitary adenoma; similar pulmonary reaction to 72-154; focal pancreatic fibrosis; pronounced chronic nephropathy; liver congested.
72-193	835	Gross: Died; subcutaneous mass 2.5 cm in diameter; hydrothorax; left atrial thrombosis; enlarged kidneys mottled in appearance; one thyroid enlarged and dark; nodular area projecting off pituitary; aorta with loss of elasticity. Microscopic: Myocardial degeneration; degeneration of myocardial vessels; atrial thrombosis; pronounced chronic nephropathy; hepatic cellular vacuolation and cyst formation; thyroid adenoma; pulmonary reaction similar to 72-154 plus focal alveolar fibrosis; subcutaneous carcinoma; pituitary not examined (adenoma?); diffuse keratitis.

APPENDIX B (Continued)

GROSS AND MICROSCOPIC OBSERVATIONS ON RATS DYING WHILE BEING USED IN INHALATION STUDY WITH ASBESTOS
(Initial Group Size 50 Male Rats)

Pathology Number	Days on Test at Time of Death	Gross and Microscopic Observations
72-196	843	Gross: Died; moderate autolysis; testes decreased in size and flaccid; red mass in one testis 5 mm in diameter; suppurative prostatitis; decrease of adipose tissue; enlarged, dark kidneys, mottled in appearance; subcapsular hepatic pale pinpoint foci, 1 mm in diameter; hydrothorax; left atrial thrombosis; enlarged thoracic lymph nodes. Microscopic: Pulmonary reaction like 72-154, plus more alveolar macrophage exfoliation and focal fibrosis of alveoli; aortic mineralization; focal amyloidosis and reticuloendothelial cell proliferation in liver; pronounced chronic nephropathy; myocardial degeneration; atrial thrombosis; suppurative prostatitis and urocystitis; vacuolation of cortical cells and adrenal hematocyst; thyroid adenoma; testicular atrophy; interstitial cell tumor of testicle.
72-197	865	Gross: Died; corneal opacity; nodular area in left lung; firm on palpation; firm nodular structure on primary bronchus, 8 mm in diameter; liver mottled in appearance with scattered subcapsular pale foci up to 1 mm in diameter; pale, pitted kidneys. Microscopic: Pulmonary papillary adenocarcinoma of lung; focal alveolar adenomatous proliferation and alveolar hyperplasia; some pulmonary reaction like 72-154 plus more alveolar fibrosis; pronounced chronic nephropathy; thyroid adenoma; secondary parathyroid hyperplasia; vacuolation of adrenal cortical cells; splenic congestion; myocardial degeneration; hepatic congestion and bile duct hyperplasia; aortic mineralization.
72-199	-	No animal available for examination, probably due to cannibalism or loss of rat.

APPENDIX C

GROSS AND HISTOPATHOLOGIC OBSERVATIONS ON NON-PULMONARY TISSUES OF MALE RATS KILLED AT 7, 8 OR 13 MONTH TIME INTERVALS DURING INHALATION STUDY WITH ASBESTOS

			Gross Observations				Histopathologic Observations											
Time Interval	Treatment Group	Number of Rats	Adrenal hematocyst	Overgrown incisor teeth	Mottled surface of kidneys	Dilatation of renal pelvis and calculi	Renal tubular cast formations	Inflammatory cell aggregates in kidney	Mineralized deposits in renal tubules	Mineralized deposits in renal pelvis	Chronic nephropathy, slight	Chronic nephropathy, moderate	Intestinal nematodiasis	Isolated aggregates of inflammatory cells adjacent to degenerate hepatocytes	Focal myocardial degeneration and inflammation	Increased splenic hemopoiesis, slight	Focal interstitial fibrosis of pancreas	Focal accumulation of pigment in pancreas
7	Control	5	0	0	0	1	5	2	2	1	0	0	1	0	0	0	0	0
7	Asbestos	5	0	0	0	0	4	0	1	0	0	0	0	0	1	0	0	0
8	Control	5	0	0	2	0	4	0	0	1	0	0	0	1	1	0	0	0
8	Asbestos	5	0	0	1	0	4	0	0	0	0	0	0	0	0	0	0	0
13	Control	5	1	0	1	0	5	5	0	0	4	1	4	1	2	3	1	1
13	Asbestos	5	0	1	1	0	5	5	0	0	5	0	3	2	1	2	0	0

Data listed as number of rats in each group showing the various observations.

APPENDIX D

CROSS AND HISTOPATHOLOGIC OBSERVATIONS ON NON-PULMONARY TISSUES OF MALE RATS KILLED AT 25 MONTH TIME INTERVAL DURING INHALATION STUDY WITH ASBESTOS

25	Time Interval in Months			
Control	Treatment Group			
4	Number of Rats Examined			
2	Corneal opacity	Gross Observations		
1	Pale, enlarged and roughened kidney			
1	Cyst in kidney			
1	Increase in size of adrenal gland			
1	Multiple pale subcapsular foci in liver			
2	Increased prominence of parathyroids			
1	Emaciation, nasal porphyrins			
1	Mineralization of gastric wall			
1	Decreased size of testes and sex glands			
1	Focal reddened area on pituitary			
1	Contraction of left hock joint			
0	Dilated renal pelvis			
0	Sucutaneous abscess			
0	Mass adjacent to urinary bladder			
0	Degeneration of myocardial blood vessels	Histopathologic Observations		
4	Myocardial degeneration, inflammation and fibrosis			
2	Decreased spermatogenesis			
2	Focal hepatic degeneration and inflammation			
0	Chronic nephropathy, moderate			
4	Chronic nephropathy, pronounced			
4	Mesenteric, testicular periarteritis			
4	Mineralization of aorta and thoracic vessels			
1	Testicular atrophy			
4	Vacuolation of adrenal cortical cells			
5	Secondary parathyroid hyperplasia			
1	Adrenal pheochromocytoma			
1	Thyroid adenoma			
1	Hyperplastic nodule of adrenal medulla			
2	Increased hematogenous pigment in spleen			
2	Increased splenic hemopoiesis			
1	Hyperplastic nodule of adrenal cortex			
1	Pituitary adenoma			
1	Focus of vacuolated hepatocytes in liver			
0	Undifferentiated sarcoma adjacent to urinary bladder and urethra			

Data listed as number of rats in each group showing the various observations.

APPENDIX E

INCIDENCE OF TUMORS IN GROUPS OF 50 MALE RATS
USED AS CONTROLS IN INHALATION STUDY WITH ASBESTOS

Morphologic Type of Tumor and Probable Origin	Days on Test at Time of Death of Rat With Tumor	Rat Number
Neural craniopharyngioma	109	72-146
Subcutaneous fibroma	186	72-134
Subcutaneous fibroma	409	72-115
Pituitary adenoma	409	72-131
Intraabdominal sarcoma	413	72-148
Pancreatic adenoma	420	72-149
Cardiac rhabdomyosarcoma	485	72-137
Subcutaneous fibroadenoma	536	72-111
Zymbal gland carcinoma	547	72-118
Pituitary adenoma	556	72-120
Subcutaneous fibroma	604	72-123
Thyroid adenoma	631	72-127
Pituitary adenoma	641	72-128
Pituitary adenoma	697	72-135
Adrenal pheochromocytoma	739	72-143
Pancreatic Adenoma	739	72-143
Adrenal pheochromocytoma	742	72-142
Thyroid adenoma	742	72-142
Pituitary adenoma	742	72-138
Adrenal pheochromocytoma	806	72-150
Pancreatic islet cell adenoma	806	72-150
Pituitary adenoma	870	72-104
Adrenal pheochromocytoma	870	72-104

Includes all tumors diagnosed in rats dying during study or at the interim kills.

APPENDIX F

INCIDENCE OF TUMORS IN GROUP OF 49 MALE RATS
USED IN INHALATION STUDY WITH ASBESTOS

Morphologic Type of Tumor and Probable Origin	Days on Test at Time of Death of Rat With Tumor	Rat Number
Pulmonary papillary adenocarcinoma	477	72-169
Adrenal pheochromocytoma	477	72-169
Pulmonary epidermoid carcinoma	554	72-157
Pulmonary epidermoid carcinoma	625	72-163
Subcutaneous neurofibroma	652	72-167
Pituitary adenoma	658	72-171
Adrenal pheochromocytoma	661	72-172
Mucinous adenocarcinoma of small intestine	661	72-172
Thyroid adenoma	661	72-172
Intraabdominal malignant schwannoma	697	72-179
Pancreatic islet cell adenoma	697	72-179
Subcutaneous fibroma	697	72-190
Adrenal pheochromocytoma	697	72-190
Pancreatic adenoma	721	72-181
Adrenal pheochromocytoma	721	72-183
Pancreatic islet cell adenoma	724	72-185
Pituitary adenoma	732	72-195
Pituitary adenoma	732	72-200
Pulmonary mucinous and adenomatous carcinoma	742	72-186
Pituitary adenoma	742	72-186
Adrenal pheochromocytoma	742	72-186
Thyroid adenoma	742	72-186
Thyroid adenoma	742	72-188

APPENDIX F (Continued)

INCIDENCE OF TUMORS IN GROUP OF 49 MALE RATS
USED IN INHALATION STUDY WITH ASBESTOS

Morphologic Type of Tumor and Probable Origin	Days on Test at Time of Death of Rat With Tumor	Rat Number
Undifferentiated sarcoma attached to urinary bladder	742	72-188
Adrenal pheochromocytoma	742	72-189
Pituitary adenoma	742	72-189
Pituitary adenoma	812	72-192
Thyroid adenoma	835	72-193
Subcutaneous carcinoma	835	72-193
Pituitary adenoma	835	72-193
Thyroid adenoma	843	72-196
Testicular interstitial cell tumor	843	72-196
Pulmonary papillary adenocarcinoma	865	72-197
Thyroid adenoma	865	72-197

APPENDIX G

MORTALITY DATA AND MAJOR GROSS AND HISTOPATHOLOGIC OBSERVATIONS IN HAMSTERS USED AS CONTROLS FOR INHALATION STUDY OF ASBESTOS

Pathology No.	Days on Test at Time of Death	Major Gross and Histopathologic Observations
72-250	366 Days	Spontaneous death; gross and microscopic evidence of enteritis and colitis; periportal hepatic inflammation and amyloidosis; amyloid nephrosis; splenic amyloidosis.
72-248	366 Days	Spontaneous death; severe autolytic changes; gross evidence of enteritis.
72-256	366 Days	Spontaneous death; diffuse periportal hepatic inflammation and amyloidosis; amyloid nephrosis; splenic amyloidosis.
72-252	367 Days	Spontaneous death; external fecal pasting of perineal area; increased fluidity of feces and ingesta in lumen of intestinal tract (bacteriological culture indicative of Salmonella-type organism); hyperemia of mesenteric vessels; nephrocalcinosis; focal hepatic inflammation and necrosis.
72-259	375 Days	Spontaneous death; gross and microscopic evidence of enteritis; decreased spermatogenesis; hyalinization of blood vessels of viscera; diffuse periportal hepatic inflammation and amyloidosis; splenic amyloidosis.
72-249	415 Days	Spontaneous death; concretion impacting lumen of stomach; enteritis; advanced autolysis.
72-246	416 Days	Spontaneous death; diarrhea, due to enteritis; periportal hepatic inflammation; nephrocalcinosis.
72-247	464 Days	Spontaneous death; hepatic biliary cysts, amyloidosis and inflammation; focal myocardial degeneration; splenic and adrenal amyloidosis; amyloid nephrosis; adrenal hematocyst; unilateral atrophy of testicle.

APPENDIX G (Continued)

MORTALITY DATA AND MAJOR GROSS AND HISTOPATHOLOGIC OBSERVATIONS IN HAMSTERS
USED AS CONTROLS FOR INHALATION STUDY OF ASBESTOS

Pathology No.	Days on Test at Time of Death	Major Gross and Histopathologic Observations
72-257	498 Days	Spontaneous death; multiple subcutaneous masses, histologically diagnosed as malignant lymphoma, with metastasis to liver, lymph nodes and testes; hepatic biliary cyst and inflammation; nephrocalcinosis; focal myocardial degeneration.
72-253	546 Days	Moribund; ascites; hepatic biliary cysts, amyloidosis and inflammation; amyloid nephrosis; focal myocardial degeneration; splenic and adrenal amyloidosis; hyalinization of visceral blood vessels; aortic medial degeneration and mineralization.
72-251	546 Days	Spontaneous death; enteritis; focal alveolar epithelial hyperplasia; increased number of alveolar macrophages, eosinophilic material and pigment within alveoli; renal, hepatic, adrenal amyloidosis; diffuse myocardial degeneration.
72-254	571 Days	Spontaneous death; enteritis; hyalinization of visceral blood vessels; splenic and adrenal amyloidosis; focal alveolar epithelial hyperplasia; pigmented material and eosinophilic material in alveoli.
72-258	577 Days	Moribund; emaciated due to purulent odontitis; biliary cysts, amyloid and pigment deposits in liver; splenic and adrenal amyloidosis.
72-255	659 Days	Spontaneous death; enteritis; hepatic biliary cysts, inflammation and amyloidosis; splenic amyloidosis; adrenal cortical adenoma; focal alveolar cellular aggregates, mostly macrophages with particles in cytoplasm; mineralized deposits and cholesterol cleft formations in lungs.

APPENDIX G (Continued)

MORTALITY DATA AND MAJOR GROSS AND HISTOPATHOLOGIC OBSERVATIONS IN HAMSTERS
USED AS CONTROLS FOR INHALATION STUDY OF ASBESTOS

Pathology No.	Days on Test at Time of Death	Major Gross and Histopathologic Observations
72-260	723	Spontaneous death; subcutaneous edema, hydrothorax and ascites; hepatic biliary cysts, amyloidosis, inflammation and pigment deposits; splenic, adrenal amyloidosis; adrenal hyperplastic nodule; amyloid nephrosis; decreased testicular spermatogenic activity; hyalinization of visceral blood vessels; diffuse myocardial degeneration; secondary parathyroid hyperplasia; pulmonary atelectasis and congestion.

APPENDIX H

MORTALITY DATA AND MAJOR GROSS AND HISTOPATHOLOGIC OBSERVATIONS IN HAMSTERS USED IN INHALATION STUDY OF ASBESTOS

Pathology No.	Days on Test at Time of Death	Major Lesions Noted at Gross and Microscopic Examination
72-237	8	Spontaneous death; autolysis and cannibalism precluded definitive evaluation of tissues.
72-238	11	Spontaneous death; enteritis; enteric cestodiasis (possibly Hymenolepis sp.); focal consolidation of lung due to inflammatory cells.
72-233	46	Spontaneous death; bullous distension of segment of left diaphragmatic lobe of lung; microscopically diagnosed as pulmonary ectatic emphysema.
72-234	66	Spontaneous death; ulcerative enteritis; periportal hepatic inflammation, focal aggregates of cells adjacent to respiratory bronchioles, including particle-laden macrophages.
72-235	86	Spontaneous death; ulcerative enteritis; adrenal cortical amyloidosis, amyloid nephrosis; hepatic periportal inflammation and amyloidosis; purulent funiculitis; decreased spermatogenic activity; ascites, hydrothorax and subcutaneous edema.
72-240	112	Moribund; purulent ophthalmitis and meningitis; adrenal lipidosis and amyloidosis; focal hepatic inflammation and lipidosis; focal areas of hypercellularity near terminal bronchioles in lungs.
72-243	123	Spontaneous death; enteritis; adrenal cortical lipidosis and amyloidosis; focal hepatic inflammation and degeneration; postmortem congestion of lungs.

APPENDIX H (Continued)

MORTALITY DATA AND MAJOR GROSS AND HISTOPATHOLOGIC OBSERVATIONS IN HAMSTERS USED IN INHALATION STUDY OF ASBESTOS

Pathology No.	Days on Test at Time of Death	Major Lesions Noted at Gross and Microscopic Examination
72-239	140	Moribund; ascites, hydrothorax and subcutaneous edema; severe amyloid nephrosis; hepatic periportal inflammation and amyloidosis; splenic amyloidosis; focal minimal hyperplasia of epithelium of terminal bronchioles; decreased spermatogenic activity; severe adrenal cortical lipidosis and amyloidosis; hyalinization of blood vessels.
72-241	294	Spontaneous death; advanced autolysis and some postmortem cannibalism; some evidence of amyloid nephrosis; adrenal cortical amyloidosis; splenic amyloidosis; decreased spermatogenesis; hyalinization of blood vessels in viscera; adrenal cortical amyloidosis; aggregates of cells, some macrophages with particles, adjacent to terminal bronchioles.
72-244	372	Spontaneous death; advanced autolysis, amyloid nephrosis; periportal hepatic inflammation and amyloidosis; aggregates of dust particles present within alveolar macrophages near terminal bronchioles of lung.
72-245	382	Spontaneous death; amyloid nephrosis; periportal hepatic inflammation and amyloidosis; adrenal cortical amyloidosis and hemorrhage; splenic amyloidosis; hyalinization of blood cessels of viscera; minimal focal areas of alveolar epithelial hyperplasia adjacent to terminal bronchioles; focal aggregates of cells, some macrophages with particles in cytoplasm, near terminal bronchioles.
72-236	434	Spontaneous death; amyloid nephrosis and nephrocalcinosis; splenic amyloidosis; periportal hepatic inflammation; decreased spermatogenesis; adrenal cortical lipidosis and amyloidosis; focal aggregates of cells, including macrophages, near terminal bronchioles; focal alveolar epithelial hyperplasia, minimal.

APPENDIX H (Continued)

MORTALITY DATA AND MAJOR GROSS AND HISTOPATHOLOGIC OBSERVATIONS IN HAMSTERS USED IN INHALATION STUDY OF ASBESTOS

Pathology No.	Days on Test at Time of Death	Major Lesions Noted at Gross and Microscopic Examination
72-242	435	Spontaneous death; severe amyloid nephrosis; splenic amyloidosisl adrenal cortical amyloidosis and hemorrhage; hepatic amyloidosis and biliary cyst formation; hyalinization of abdominal blood vessels; interstitial amyloidosis of thyroid; focal aggregates of cells, including macrophages, near terminal bronchioles.
72-232	445	Spontaneous death; advanced autolysis; severe amyloid nephrosis; adrenal cortical amyloidosis and hemorrhage; periportal hepatic inflammation and amyloidosis, focal myocardial degeneration.
72-231	455	Spontaneous death; autolysis, hepatic amyloidosis and inflammation; amyloid nephrosis; focal myocardial degeneration; no fibrosis or tumor formation in autolyzed lung; adrenal amyloidosis.

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