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MELLON INSTITUTE

Special Report

The Fibrogenic Potential of Asbestos Products via Intraperitoneal Injection in Guinea Pigs, Rats and Rabbits and by the Intratracheal Route in the Rat

Chemicals Division, Union Carbide Corporation Industrial Fellowship 274-29

Summary

The results of intraperitoneal administration indicate that the asbestos products studied produced fibrotic lesions of the visceral organs in rats and guinea pigs regardless of fiber length. Of the three products, CMS-100 (refined fiber), produces the most severe reaction. JT-100 (standard fiber) and JM-3K (Johns Manville screened fiber) produced similar but less severe reactions. The results on rabbits were inconclusive.

Both JT-100 and CMS-100 produced specific lesions in rats by the intratracheal route but with JT-100 they were more severe. No lesions were found in the rats which received JM-3K fibers.

These results indicate that these three asbestos fibers may be fibrogenic by either route. No specific lesions were observed in the lungs of the JM-3K intratracheal rats, but only two rats survived to be examined.

Samples

The following samples were shipped to Mellon Institute at the request of Mr. Paul W. McDaniel who furnished the descriptive information.

Designation of Asbestos Product	Source	Quantity	Date Received	M. I. Sample Number
*CTS-100 Fiber (same as JT-100 Fiber) "Standard Fiber" containing impurities in the form of clay and magnetite. A short fiber.	Sterling Forest	8 oz.	8-14-63	26-220
*CMS-100 Fiber "Refined Fiber" with lesser impurities than JT-100. A short fiber.	Sterling Forest	8 oz.	8-14-63	26-219

* The individual fibers for most part had lengths of 0.9 to 10 microns, but there were some as long as 30 microns and some that were less than 0.5 micron. The diameters of the fiber were generally 0.3 to 1.2 microns, but there were smaller sizes noted. The clay-magnetite particles were mostly 0.5 to 3.0 microns in diameter but there were some present as small as 0.08 micron (by electron microscope).

Designation of Asbestos Product	Source	Quantity	Date Received	M. I. Sample Number
JM-3K Fiber. "Long Fiber" (Brushed through screen to reduce fiber length to 1 mm. or less before injecting.)	Manville, N.J.	8 oz.	8-26-63	26-227

Intraperitoneal Injections

Methods

The JM-3K asbestos was brushed through a 1 mm. screen to reduce its fiber length to < 1000 micra (1.0 mm.) in order to facilitate dosing. The CMS-100 and JT-100 asbestos samples were used as received. Each asbestos product was prepared as a 2.5% (W/V) suspension in 0.85% saline. All needles, syringes and suspensions were sterilized prior to use. The animals were divided into three groups--each consisting of eleven male albino guinea pigs (P), six male albino rats (R), and two male albino New Zealand rabbits (H). The guinea pigs and rabbits received intraperitoneal injections of 2 ml. (50 mg.) and the rats, 1 ml. (25 mg.) of the respective asbestos suspensions. Eleven guinea pigs and six rats received control intraperitoneal injections of saline. There were no rabbit controls. All injections were made in the lower right quadrant of the abdomen. Tables 29-92 through 29-95 contain the results on individual animals.

Results

CMS-100 produced the most severe reaction in the form of granulomas with giant cells in six of the seven guinea pigs examined micropathologically. Typical granulomas with giant cells were observed in three of four rats and the one rabbit.

JT-100 asbestos fiber produced a granulomatous reaction in all of the 8 guinea pigs as well as the one rat subjected to micropathological examination. The rabbits had incidental lesions unrelated to the asbestos fibers.

The JM-3K asbestos fibers produced granulomas with fibers visible in five of the five guinea pigs examined. One of two rats had granuloma formation which was visible on gross examination.

Intratracheal Injections

Methods

One per cent (W/V) suspensions of JT-100, CMS-100 JM-3K and a 0.5% suspension of CMS-100 were prepared in 0.85% saline as for the intraperitoneal injections.

Female albino rats weighing in excess of 200 grams were given 1 ml. of the respective asbestos suspensions by intratracheal injection. The rats were anesthetized with saturated vapor of anhydrous diethyl ether. The trachea was exposed by blunt dissection and the injection was made directly and the incision closed with a Michael Wound Clamp.

Eight rats were injected with 1 ml. of a 1% JT-100 suspension (10 mg. asbestos). Eight rats were injected with 1 ml. of a 1% JM-3K suspension (10 mg. asbestos). Because of the flocculent properties of CMS-100, only three rats were dosed with 1 ml. of a 1% suspension (10 mg. asbestos). Eight rats were injected with 1 ml. of a 1% CMS-100 suspension (5 mg. asbestos). Six rats injected with physiological saline served as controls. Tables 29-96 through 29-99 contain results on individual animals.

Results

Specific lesions were found in most of the rats given CMS-100 and JT-100 that consisted of marked granuloma formation with bluish foreign body material present (magnetite?). Marked bronchiolitis obliterans was noted in most rats, also with bluish foreign body material within the lesions. The JT-100 rats had a more severe fibrotic reaction to this foreign material. Multinucleate giant cells were a common feature with the granulomas of the JT-100 rats but were conspicuously absent in the lungs of the rats given CMS-100. Micropathology was performed on only two rats receiving JM-3K asbestos. Neither of these animals had lesions similar to JT-100 or CMS-100.

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Table 29-92

Intraperitoneal Injections of Asbestos CMS-100

Dose of Asbestos	Animal Number	Days to Death or Sacrifice	Gross Pathology	Micropathology
50 mg. (2 ml. of 2.5% suspension)	P. 96813	20 D	Peritonitis; asbestos scattered throughout abdominal cavity.	Not examined.
	P. 96803	75 D	Peritonitis; adhesions of intestines to liver.	Not examined.
	P. 96815	240 D	Autolyzed.	Not examined.
	P. 96806	270 D	No asbestos in abdominal cavity.	Not examined.
	P. 96802	286 S	Multiple small adhesions of the omentum to the mesentery.	Several small, well marked granulomas with giant cells on the serosal surface of colon.
	P. 96807	286 S	Adhesions of liver to stomach. Deposits scattered in the intestinal mesentery.	Liver--marked granulomatous reaction on the surface. Granulomas--serosal wall.
	P. 96810	286 S	Omentumal adhesions to liver with deposits in the omentum.	Liver--well marked granulomas. Marked chronic granulomas in the intestine and diaphragm.
	P. 96811	286 S	Intestinal adhesions to midline and seminal vessels.	Intestinal, liver, skeletal muscle--adhesions to each other. Areas of giant cell formation.
	P. 96812	286 S	Areas of fibrosis in most of left liver lobes.	Colon--large cystic masses filled with debris. Lined by columnar epithelium.
	P. 96814	286 S	Adhesions--liver to stomach and intestines.	Liver--fibrosis and granuloma formation. Foreign body granulomas on abdominal wall.
	P. 96821	286 S	Adhesions of abdominal wall to liver, stomach and omentum with deposits.	Granulomatous lesions of the stomach, liver and skeletal muscle.
	H. 96737	60 D	Numerous deposits of asbestos adherred to intestines.	Not examined.
	H. 96574	270 S	Multiple adhesions, ventral colon and urinary bladder.	Multiple well encapsulated granulomas present with innumerable giant cells.

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Table 29-9.

(Continued)

)ose of Asbestos	Animal Number	Days to Death or Sacrifice	Gross Pathology	Micropathology
:5 mg. (One ml. of 2.5% :uspension)	R. 4571	20 D	Congested lungs and liver; asbestos scattered throughout abdominal cavity.	Not examined.
	R. 4678	170 D	Asbestos deposits throughout abdominal area.	Not examined.
	R. 4629	258 S	Nodules of white material in mesentery, ventral and abdominal wall.	Scattered granulomas in intestine and skeletal muscle.
	R. 4631	258 S	Deposits in the mesentery and ligaments of the testicle.	Multiple granulomas with giant cells and asbestos deposits.
	R. 4634	258 S	Chronic abscess pneumonia.	Chronic bronchopneumonia.
	R. 4660	258 S	Scattered deposits in mesentery and wall of small intestines. Adhesion of testes to intestines.	Large granulomas, well encapsulated.

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Table 29

Intraperitoneal Injections of Asbestos JT-100

Dose of Asbestos	Animal Number	Days to Death or Sacrifice	Gross Pathology	Micropathology
50 mg. (2 ml. of 2.5% suspension)	P. 96844	11 D	Peritonitis, asbestos scattered throughout abdominal cavity.	Not examined.
	P. 96851	150 D	Entire gut adherred together. Liver adherred to ventral wall and diaphragm.	Not examined.
	P. 96849	185 D	Multiple visceral adhesions of the asbestos to the ventral abdominal wall.	Not examined.
	P. 96834	286 S	Gray deposits in the ventral abdominal wall.	Scattered foreign body granulomas with slightly elongated fibers of asbestos in them.
	P. 96835	286 S	Severe multiple adhesions with pus incorporated.	Typical granulomas.
	P. 96837	286 S	Multiple intestinal adhesions. Gray deposits in the abdominal wall.	Adherred masses with many granulomas on the serosal surface.
	P. 96839	286 S	Omental adhesions to the liver with tiny deposits in this mesentery.	Typical connective tissue granulomas.
	P. 96840	286 S	Spleen adherred to ventral wall, stomach to diaphragm.	Typical connective tissue granulomas.
	P. 96841	286 S	Multiple tiny deposits on left liver lobes and left abdominal wall.	Numerous granulomas with foreign bodies present in them.
	P. 96847	286 S	Omental adhesions to the ventral tips of the liver.	Typical granulomas with foreign bodies, giant cells, fibrosis present.
	P. 96848	286 S	Deposits on the intestinal mesentery and abdominal wall with omental adhesions.	Typical connective tissue granulas.
	H. 96729	270 S	Heart covered by chronic connective tissue.	Essentially normal.
	H. 96734	270 S	Multiple serosal deposits scattered primarily on the colon and ventral wall.	Essentially normal.

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Table 29-93

(Continued)

Dose of Asbestos	Animal Number	Days to Death or Sacrifice	Gross Pathology	Micropathology
25 mg.	R. 4576	36 D	Cannibalized.	Not examined.
(One ml. of 2.5%	R. 4536	160 D	Autolyzed.	Not examined.
suspension)	R. 4534	200 D	Peritonitis, pleuritis, some fibrosis in pleural cavity.	Not examined.
	R. 4617	242 D	Pneumonia. Asbestos particles scattered throughout entire abdominal cavity.	Not examined.
	R. 4596	258 S	Slight deposits in the mesentery and omentum.	Intestine--typical granulomas with foreign bodies.

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Table 2[illegible] 4

Intraperitoneal Injections of Asbestos JM-3K

Dose of Asbestos	Animal Number	Days to Death or Sacrifice	Gross Pathology	Micropathology
50 mg. (2 ml. of 2.5% suspension)	P. 96829	18 D	Peritonitis, asbestos adherred to ventral wall and small intestine.	Not examined.
	P. 96833	43 D	Intestines adherred to ventral wall.	Not examined.
	P. 96830	64 D	Scattered adhesions to ventral abdominal wall.	Not examined.
	P. 96826	76 D	Peritonitis, liver and stomach adherred to ventral abdominal wall.	Not examined.
	P. 96828	78 D	Peritonitis, asbestos scattered throughout abdominal cavity.	Not examined.
	P. 96832	86 D	Intestines adherred to ventral abdominal wall. Abscessed at point of adhesion.	Not examined.
	P. 96822	286 S	Multiple adhesions of the liver to the stomach, omentum, and intestines.	Foreign bodies. Granuloma attached to intestinal wall. Some granulomas in liver.
	P. 96823	286 S	Deposits on right seminal vessel.	Seminal vessel--granulomatous reaction with foreign material in soft tissue and mesentery.
	P. 96824	286 S	Greenish deposits in the ventral abdominal wall and omentum with adhesions to liver.	Foreign body granulomas with foreign material present.
	P. 96827	286 S	Midline omental adhesions to greenish deposits.	Deposits of foreign material and large granulomas on muscle.
	P. 96831	286 S	Liver adherred to ventral abdominal wall.	Tip of liver infectious; abscess formation, granuloma formation.
	H. 96764	60 D	No asbestos in peritoneal cavity.	Not examined.
	H. 96697	270 S	Asbestos at site of injection.	Essentially normal.
25 mg. (One ml. of 2.5% suspension)	R. 4628	35 D	Pneumonia. Intestine adherred to the ventral wall.	Not examined.
	R. 4622	230 D	Pasturella Pneumonia. Intestines adherred to abdominal wall with each other.	Not examined.
	R. 4623	234 D	Autolyzed.	Not examined.
	R. 4615	241 D	Pasturella Pneumonia.	Not examined.
	R. 4578	258 S	Adhesions of the omentum and mesentery.	Essentially normal.
	R. 4583	258 S	Middle ear infection.	Essentially normal.

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Table 29-95

Intraperitoneal Injections of Saline Control

Dose of Saline	Animal Number	Days to Death or Sacrifice	Gross Pathology	Micropathology
2 ml.	P. 96857	88 D	Pneumonia.	Not examined.
	P. 96856	156 D	Pneumonia.	Not examined.
	P. 96853	170 D	Pneumonia.	Not examined.
	P. 96858	207 D	Pneumonia.	Not examined.
	P. 96852	286 S	Essentially normal.	Essentially normal.
	P. 96859	286 S	Essentially normal.	Scattered areas of interstitial pneumonia.
	P. 96860	286 S	Emaciated. Liver massively reduced in size.	Liver necrosed and abscessed.
	P. 96861	286 S	Essentially normal.	Essentially normal.
	P. 96862	286 S	Essentially normal.	Essentially normal.
	P. 96863	286 S	Chronic nephritis in both kidneys.	Chronic interstitial nephritis.
	P. 96864	286 S	Essentially normal.	Essentially normal.
One ml.	R. 4484	12 D	Pneumonia.	Not examined.
	R. 4483	258 S	Chronic abscessed pneumonia.	Massive abscessed pneumonia.
	R. 4531	258 S	Essentially normal.	Essentially normal.
	R. 4540	258 S	Essentially normal.	Essentially normal.
	R. 4542	258 S	Essentially normal.	Essentially normal.
	R. 4557	258 S	Essentially normal.	Essentially normal.

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Table 29-96

Intratracheal Injections of Asbestos CMS-100 to Rats

Dose of Asbestos	Rat Number	Days to Death or Sacrifice	Gross Pathology	Micropathology
10 mg. (One ml. of 1% suspension)	84636	30 S	Pneumonia.	Pneumonia, numerous granulomas scattered throughout lung.
	84645	90 S	Pneumonia.	Pneumonia, lesions of bronchiolitis obliterans in several bronchi and bronchioles.
	84702	180 S	Chronic pneumonia.	Scattered granulomas; lesions of bronchiolitis obliterans with foreign material and thrombotic-like areas.
5 mg. (One ml. of 0.5% suspension)	72531	12 D	Cannibalized.	Not examined.
	81427	30 S	Lung--appeared normal.	Multiple granulomas; bluish material present in all granulomas.
	81433	90 S	No lesions.	Scattered small granulomas. Some bronchiolitis obliterans also apparent.
	81440	90 S	Chronic pneumonia.	Pneumonia; scattered granulomas; bronchiolitis obliterans.
	72528	180 S	Not recorded.	Scattered small granulomas.
	77679	180 S	Lipid foci in lungs.	Bronchiolitis obliterans. Chronic granulomas sans giant cells.
	77680	180 S	Gray foci in lungs.	Numerous scattered granulomas.
	81600	180 S	Pneumonia.	Multiple granulomas scattered throughout lung. Bronchiolitis obliterans.

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Table 2[illegible] 7

Intratracheal Injections of Asbestos JT-100 to Rats

Dose of Asbestos	Rat Number	Days to Death or Sacrifice	Gross Pathology	Micropathology
10 mg. (One ml. of 1% suspension)	84629	60 D	Large white areas on lung; atelectasis of the right lung.	Bronchiectasis. Areas of acute bronchopneumonia.
	84672	123 D	Pneumonia.	Not examined.
	84669	151 D	Pasturella Pneumonia.	Not examined.
	84633	30 S	Chronic pneumonia.	Multiple granulomas and bronchiolitis obliterans.
	84659	30 S	Chronic pneumonia.	Pneumonia; granulomas, large lesions of bronchiolitis obliterans.
	84674	90 S	Pneumonia.	Numerous granulomas, well marked bronchiolitis obliterans.
	84676	90 S	Chronic abscessed pneumonia.	Scattered granulomas.
	84631	180 S	Not recorded.	Granulomas, some bronchiolitis obliterans.

Table 29-98

Intratracheal Injections of Asbestos JM-3K to Rats

Dose of Asbestos	Rat Number	Days to Death or Sacrifice	Gross Pathology	Micropathology
10 mg. (One ml. of 1% suspension)	84695	10 D	Entire lung was dark red.	Not examined.
	84635	13 D	Chronic pneumonia.	Not examined.
	81214	15 D	Pneumonia and emphysema.	Not examined.
	81171	50 D	Chronic pneumonia; bronchial lymph nodes, enlarged and gray.	Not examined.
	81161	30 S	Chronic pneumonia.	Chronic bronchopneumonia.
	84660	180 S	Chronic pneumonia and enlarged lymph nodes.	Chronic bronchopneumonia, a few scattered granulomas.

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Table 29-99

Intratracheal Injections of Saline to Rats

Dose of Saline	Rat Number	Days to Death or Sacrifice	Gross Pathology	Micropathology
One ml.	78253	30 S	Essentially normal.	Essentially normal.
	78273	30 S	Essentially normal.	Essentially normal.
	78302	90 S	Essentially normal.	Essentially normal.
	78717	90 S	Azygous abscessed.	Few areas of chronic pneumonia.
	84639	180 S	Essentially normal.	Essentially normal.
	84646	180 S	Essentially normal.	Essentially normal.
	84651	180 S	Essentially normal.	Essentially normal.
	84677	180 S	Essentially normal.	Essentially normal.

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