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Brief Summary

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Polyvinyl chloride (PVC) is widely used in various forms. Rigid PVC is used for tubing and fittings (insulation material and drainage pipe), foils, films and sheeting (packaging, recording tapes), profiles (blinds, window frames), tiles, sound records, and fibers. Flexible PVC is used for cables, foils (decoration, roof covering), tubing, artificial leather, flooring, foam rubber, paint, varnish (lacquer), and toys.

Reports of pulmonary dysfunction and pneumoconiosis in PVC workers and dust exposed animals point to the need for further studies on the toxicological properties of the polymer. Also, cases of still-births, miscarriages and malformations among workers engaged in the polymerization of vinyl chloride have aroused great interest in the toxicological properties of PVC. Since PVC is a fine volatile dust, pathogenic effects of the lungs may be anticipated.

B. F. Goodrich Company is a supplier of resins for vinyl dispersions using the trade name "Geon." The dispersions are fluid suspensions of special fine particle-size polyvinyl chloride resins in plasticizing liquids. When the system is heated to about 148 to 177°C (300 to 350°F), fusion (mutual solubilization of resin and plasticizer) takes place. The dispersion turns into a homogeneous hot melt. When the melt is cooled below 50 to 60°C (122 to 140°F), it becomes a tough vinyl product.

The term "plastisol" is used to describe a vinyl dispersion which contains no volatile thinners or diluents. Plastisols often contain stabilizers, fillers, and pigments along with the essentials, dispersion resin and liquid plasticizer, but all ingredients have very low volatility under the processing and use conditions.

Geon 121 is a high molecular weight resin. It has been the standard of the plastisol industry for over 25 years and is an excellent resin for starting point formulations. Currently, it is being used in dip, slush and rotational molding, spread coating, foam coating and molding, crown and jar seals, and caulks and sealants.

In light of the relationship unequivocally established between occupational exposure to vinyl chloride monomer and liver angiosarcoma, and the concern expressed on potential risks to human health from exposure to polyvinyl chloride (PVC) dusts manufactured and used from polymerization of the vinyl chloride monomer, DBBS in FY'75 in its project plan on "Chronic Exploratory Toxicology Studies and Test of Validity of Industrial Air Standards" proposed an inhalation exposure study with PVC dust. Actual exposures to a representative material (B. F. Goodrich Company, Geon 121) began in February 1976 utilizing three species of animals -- monkey, guinea pig and rat -- a 6-6-1/2 hours per day, 5 days per week exposure regimen, and at a 10 mg/m^3 respirable PVC dust concentration. Exposure duration was for 22 months. The following table summarizes the above data.

Selected Data from PVC Chronic Inhalation Exposure Study (Geon 121)

Animal Species	No. per Group		Duration of Exposure			Mean PVC Conc.	Mean Range of Conc.	CT Values (mg/m^3-Hrs.)	
	Exposed	Control	Calendar Days	Exposure Days	Exposure Hrs.	mg/m^3	mg/m^3	Intended	Actual
Monkey	10	10	690	464	2818	10.8	7.5-12.3 ~~4.65 9.25~~	28,180	30,510
Guinea Pig	40	40	379	245	1428	10.6	-	14,700	14,698
Rat	80	80	376	244	1424	10.6	-	14,640	14,627

Particle size analysis of collected exposure chamber samples indicated that the generated PVC dust was of a geometric mean diameter of 0.53μm with more than 99% of the sampled particles below 5.0μm; 82% below 1.0μm. The manufacturer's specifications data states a particle size range for Geon 121 of between 0.5 and 1.5μm.

Exposure System: Chambers used in the study were five feet square, stainless steel, and featured a dynamic airflow system of 40 cubic feet per minute under a negative chamber pressure of approximately 0.2" H_2O. The PVC aerosol was generated by means of a Wright Dust Feed Mechanism and the dust dispersed into the chamber at a rate sufficient to maintain the desired 10 mg/m^3 concentration. Gravimetric analyses were made four times per day on collected membrane filter samples for total dust concentrations, and once per day for respirable dust (10-plate horizontal elutriator sample).

Biological response data evaluated from the exposed and control animals at time of serial sacrifice/evaluation included:

Biochemical/Clinical Chemistry (Guinea Pig, Rat only): (SGOT, SGPT, alkaline phosphatase, gamma glutamyl transpeptidase, total protein and serum protein electrophoresis). No significant differences were indicated in rats for any parameter. Guinea pig data showed controls with higher SGOT, SGPT, and alkaline phosphatase. It was concluded that no extensive liver damage was detected by any of the liver clinical indicator tests used. However, a sizable amount of liver damage must occur before these tests would indicate abnormalcy. One cannot conclude that there is no liver damage; but only that there is no extensive liver involvement.

Pathology (All species): No significant alterations in liver tissue. The only contribution of the inhaled PVC dust deposition and retention to pulmonary tissue morphology was aggregation of PVC-containing macrophages (refer to attached pathology reports and to report on Amorphous Silica exposed and control monkeys).

Pulmonary Function (Monkey only): Fasted, exposed and control monkeys were tested for pulmonary function one day following their last exposure. Evaluations were accomplished through use of a variable pressure, whole-body plethysmograph. Tests evaluated were: Total lung capacity (TLC); vital capacity (VC); inspiratory capacity (IC); residual volume (RV) divided by total lung capacity (RV/TLC); forced expiratory volume in 0.5 seconds (FeV 0.5); forced expiratory volume in 1.0 seconds (FeV 1.0); peak expiratory flow (PF); maximum mid expiratory flow (MMF); maximum expiratory flow volume curves (MEFV) at 50%, 25% and 10% of vital capacity; resistance; and compliance.

A summary of the extensive pulmonary function evaluations indicated some signs of loss of lung recoil pressure, probably a result of the animals' aging process. In most cases differences were noted during the second and third testing periods (exposure months 6 and 14) and were indicative of some small airway obstruction. At this time, however, these differences were not statistically significant. At the last evaluation (month 22) compared with baseline (pre-exposure) data there were no significant differences for any parameter tested. Impairment of respiratory function does not appear to be indicated under the conditions of this study from exposure to respirable PVC dust.

Attachments

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

TO : Chief, BSB
THROUGH: Chief, Pathology Section _____

DATE: May 5, 1977

Dr. Gi... 23

FROM : Veterinary Pathologist, Pathology Section

SUBJECT: Pathology Report on Rats Exposed to PVC

R&S 112892

Male rats were exposed by inhalation to polyvinyl chloride (PVC), respirable concentration 10 mg/m^3, for 6 hours/day for 5 days/week for a period of 12 months. The animals were sacrificed immediately after 12 months of exposure to PVC. The following tissues on each animal were saved at necropsy for histopathology evaluation: lungs, liver, heart, spleen, kidney, pancreas, adrenal, thyroid, testis, and urinary bladder. The histopathology evaluation was performed on a total of 121 (exposed 57, control 64) male rats.

1.1 Rats exposed to PVC 10 mg/m^3 for 6 hours/day for 5 days/week by inhalation.

Path. Accs. No.: 76-1329, 76-1337, 76-1338, 76-1340 to -1393.

Gross pathology:

Lungs: Multiple white foci of varying size either in one or more lobes of the lungs were seen in 76-1337, -1338, -1344, -1345, -1347, -1348, -1350, -1353, -1354, -1363, -1367, -1369, -1373, -1379, -1385, and -1387. "Abscess" was seen in the lungs of each of 76-1346, -1351, -1352, -1363, and -1378. "Tumor" measuring 1.5 x 2.0 cm and weighing 2.90 gm was seen in 76-1375.

Liver: Enlarged dark red liver was seen in 76-1337.

Kidney: Small mineralized areas (stones) were seen in the kidneys of 76-1363 and 76-1366.

Pituitary gland: Enlarged (10X) pituitary was seen in 76-1338.

Histopathology:

Lungs: The lesions commonly associated with the chronic murine pneumonia (bronchiectasis, peribronchial, and perivascular accumulations of lymphocytes, focal chronic active bronchitis and bronchiolitis, focal atelectasis) were seen in all rats. Vascular (arterial) wall mineralization was seen in all rats. Focal intense macrophage accumulations (solid sheets), sometimes displacing the normal structures, were seen. Most of these macrophages had varying size globular to spherical structures in the cytoplasm (foam cells).

These dense conglomerations of macrophages were occasionally associated with mild blue staining (mucin?) fluid material. The above-mentioned macrophages or macrophages surrounded by fluid when accumulated at the periphery of the lung probably imparted the appearance of "white foci" grossly seen in the lungs. The intracellular material in these macrophages was probably particles of the PVC. No birefringence was seen among these. Dr. Stettler and Mr. George Mackay informed me that these, indeed, were PVC particles, based on electron probe analysis of some lungs from the rats exposed to PVC by inhalation as well as by intravenous injection. The macrophage accumulations apart from physical displacement of the lung parenchyma do not seem to bestow any deleterious effects on these rats. No alterations (hyperplasia, etc.) of the alveolar or bronchial epithelium attributable to treatment were seen in these rats.

Tracheobronchial lymph nodes (TBLN): Macrophage accumulations as seen in the lungs were seen in the medulla and cortex of all the TBLNs examined. Reactive hyperplasia of germinal centers was also seen.

Liver: Mild fatty infiltration of hepatocytes was seen in 76-1338. Extra medullary hematopoiesis (mild) was seen in 76-1364 and 76-1371.

Spleen: Macrophages containing yellow granular material in the cytoplasm and extramedullary hematopoiesis were seen in all the spleens examined.

Heart: Mild focal myocarditis was seen in 76-1337, -1363, and -1377.

Kidney: Multifocal mineralized areas of the tubules or the transitional epithelium of the kidney pelvis were seen in 76-1348, -1353, -1356, -1363, and -1366. Focal tubular dilatation, focal tubular epithelial degeneration and regeneration and mild lymphocyte accumulations were seen in 76-1351, -1356, -1357, -1363, -1370, -1376, -1381, -1382 to -1384, -1387, -1388, -1390 to -1392.

Pancreas: Mild hyperplasia of the islets of Langerhans was seen in 76-1355, -1361, -1363, -1364, -1367, -1368, -1370 to -1372, -1376, -1377, -1379 to -1381, -1385 to -1389, and -1391 to -1393.

Adrenal: Moderate fatty infiltration of the epithelium of the cortex was seen in 76-1341 to -1344, -1348 to -1350, -1369, -1370, -1378, and -1381. An adrenal cortical adenoma was seen in each of 76-1365 and 76-1371. A pheochromocytoma was seen in 76-1358.

Thyroid: Cyst(s) containing keratin was seen in 76-1337, -1338, -1341, -1342, -1345, -1346, -1353, -1355 to -1357, -1360, -1361, -1364, -1365, -1370, -1372, -1374, -1375, -1379 to -1382, -1388, -1391 to -1393.

Testis: Vessel (artery) wall mineralization was seen in 76-1358, -1378, -1385, and -1390. Mild hyperplasia of interstitial cells and atrophy of seminiferous tubules were seen in 76-1347, -1353, -1358, -1361, -1365, -1370, and -1378.

Lymph node: Chronic lymph adenitis was seen in 76-1375. The lymph node was adjacent to a major artery suggesting it to be a mediastinal lymph node.

Pituitary: A chromophobe adenoma was seen in 76-1338.

All the other organs examined were unremarkable.

1.2 Untreated Male Rats

Path. Accs. No.: 76-1394 to -1431, 76-1510 to -1520, 76-1523 to -1537, 76-1539 to -1548.

Gross pathology: A cataract of the right eye was seen in 76-1396. Consolidation of lung lobes was seen in 76-1395, -1400, -1416, -1527, -1530, -1537, -1540, -1546, and -1547. Brown discoloration (76-1405) and an abscess was seen in the lungs (76-1418). A multiloculated mass 2.5 x 3.0 cm was seen attached to mesentery in 76-1427. Renal calculi were seen in 76-1518.

Histopathology:

Lungs: The morphological changes associated with the chronic murine pneumonia and pulmonary vascular wall mineralization as seen in 1.1 were seen in all rats. Macrophage accumulations of far lesser degree in intensity were seen in all rats. These macrophages did not congregate in a solid sheet as seen in 1.1. The cytoplasm of most of these macrophages contained granular eosinophilic material. No alveolar or bronchial epithelial hyperplasia was seen in any rat.

TBLN: Chronic reactive hyperplasia was a common finding in all rats.

Liver: A single cyst was seen in each of 76-1397 and 76-1399.

Spleen: The changes seen were similar to those seen in 1.1 in all rats.

Heart: Mild focal myocarditis was seen in each of 76-1401, -1402, -1405, -1407, and -1415.

Pancreas: Mild hyperplasia of endocrine elements was seen in 76-1395 to -1399, -1402, -1404 to -1410, -1414 to -1418, -1420, -1421, -1424 to -1426, -1428, -1429, -1510, -1511, -1514, -1515, -1518 to -1523, -1532, -1539 to -1542, and -1545.

Kidney: Tubular epithelial degeneration and regeneration, occasional tubular dilatation and focal mild lymphocytic accumulation were seen in 76-1394, -1396, -1397, -1399, -1401 to -1403, -1405, -1409, -1412, -1417 to -1419, -1421, -1422, -1425, -1431, -1515, -1524, -1527, -1534, -1546, and -1548. Focal mineralization of tubular epithelium and/or the transitional epithelium of the renal pelvis was seen in 76-1518, -1527, and -1533.

Adrenal: Adenoma of the adrenal cortex was noticed in 76-1400, -1518, -1523, and -1544. Pheochromocytoma was seen in 76-1548. Moderate fatty infiltration of the cortex was seen in 76-1410 and 76-1544.

Thyroid: Cyst(s) containing keratin was seen in 76-1395, -1397, -1399, -1402, -1403, -1406, -1410 to -1412, -1416, -1417, -1419, -1420, -1422, -1423, -1425 to -1427, -1429, -1510, -1512 to -1515, -1517, -1519 to -1527, -1529, -1530, -1532 to -1534, -1536, -1541, -1543 to -1548.

Testis: Atrophy of seminiferous tubules and Leydig cell hyperplasia was seen in 76-1395, -1400, -1514, -1516, -1533, -1541, and -1548. Vessel (artery) wall calcification was seen in 76-1398 and 76-1533. Focal moderate mineralization of seminiferous tubules was seen in 76-1418, -1510, and -1517.

Eye: 76-1396: Retinal atrophy - unilateral. Adhesions between the retina and lens with dystrophic calcification at some foci. The lens protein was well oriented with occasional basophilic bodies, probably nuclei from decidual lens cells. The calcific deposits coupled with the hyalinization of sclera imparted the opacity to the lens; cataract seen grossly.

Mass: 76-1427: Granuloma of mesenteric fat.

Comment: For comparison, this comment shall include rat and guinea pig data. Both the rats and the guinea pigs exposed to PVC by inhalation exhibited the presence of PVC particulates in the pulmonary macrophages, although the pattern of macrophage accumulation between the two species differed. There was no inflammatory or any other deleterious effect seen in the lungs of these animals that could be attributable to PVC inhalation.

The incidence of perivascular lymphoid aggregations in the lungs of guinea pigs was similar in both exposed and controls. The presence of bony spicules in the lungs of exposed and control guinea pigs was observed. The pathogenesis of these two conditions is not known (Thompson, S. W., Hunt, R. D. et al: Am. J. Path. 40:507-517 (1962); Kaufman, A. F.: Lab. Anim. Care 20:1002-1003 (1970)) and is worth exploring as NIOSH uses guinea pigs as

one species of animals in biological experiments. The nephrocalcinosis seen in the exposed and control guinea pigs may be related to diet (J. C. Woodard: Am. J. Path. 65:253-268 (1971) and 65:269-278 (1971)). Corollary to the above observation was the finding of invariable fatty infiltration of exocrine and endocrine elements of the pancreas in both the exposed and control guinea pigs and the hyperplasia of islets of Langerhans seen in both the rats and the guinea pigs employed in this experiment. In addition, the vascular wall calcification in the pulmonary vessels of rats is disturbing. All of these "incidental" findings strongly suggest that these animals had metabolic problems probably related to the animal diet. The changes seen in the testes of rats were non-specific and probably not related to treatment. The incidence of neoplasms in the adrenals of rats is within the normal range observed for Sprague-Dawley rats of this age.

Choudari Kommineni, D.V.M.

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

TO : Chief, BSB
THROUGH: Chief, Pathology Section _____

DATE: May 10, 1977

(24)

Dr. Gilliam

FROM : Veterinary Pathologist, Pathology Section

SUBJECT: Pathology Report on Guinea Pigs to PVC

Male guinea pigs were exposed by inhalation to polyvinyl chloride (PVC), respirable concentration 10 mg/m^3, for 6 hours/day for 5 days/week for a period of 12 months. The animals were sacrificed immediately after 12 months of exposure to PVC. The following tissues on each animal were saved at necropsy for histopathology evaluation: lungs, liver, heart, spleen, kidney, pancreas, adrenal, thyroid, testis, and urinary bladder. The histopathology evaluation was performed on a total of 75 (exposed 36; control 39) male guinea pigs.

2.1 Guinea pigs exposed to PVC 10 mg/m^3 for 6 hours/day for 5 days/week by inhalation.
Path. Accs. No.: 76-1432 to 76-1467.
Gross pathology: Yellow specks were seen in the lungs of 76-1434, -1436, -1459, and -1464. Consolidation of lungs was observed in 76-1435, -1437, -1439, and -1449. Small areas of necrosis in the liver of 76-1443 were seen. Mesenteric fat necrosis was found in 76-1438 and 76-1441.
Histopathology:

Lungs: All guinea pigs exhibited moderate amount of eosinophilic serous exudate mixed with mild to moderate numbers of epithelial cells (decidual showing varying stages of degeneration) in the bronchial lumens. Another common finding among all guinea pigs was the presence of multiple aggregates of lymphocytes. Most of these lymphoid aggregates were oriented around or near small arteries or veins, thus giving an appearance of lymphoid follicles. The interstitium of all the lungs showed numerous macrophages. These macrophages contained spherical to globular hollow structures in the cytoplasm. These macrophages did not aggregate in the same fashion as those seen in rat lungs (1.1). Plant material with or without associated inflammation was seen in bronchioles of 76-1432 and 76-1435. Bone formation (small spicules) in alveolar area was seen in 76-1434, -1435, -1438, -1446, -1452, -1453, -1455, and -1456. Focal atelectasis was seen in the lungs of all guinea pigs examined.

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Liver: Mild fatty infiltration of hepatocytes was seen in 76-1432, -1441, and -1467. The histology slides from 76-1443 did not show any hepatic necrosis. Search for liver tissue with necrotic areas from "wet tissue" was not fruitful.

Heart: Focal mild myocarditis was seen in 76-1441, while 76-1449 showed focal mineralization of myocardial muscle bundles.

Spleen: Macrophages with yellow granular pigment in the cytoplasm were seen in all guinea pigs.

Kidney: Multifocal mild mineralization of tubular epithelium was seen in 76-1432, -1437 to -1448, -1450 to -1460, -1462 to -1465, and -1467.

Pancreas: Fatty infiltration of the endocrine and exocrine elements was seen in 76-1439, -1442, -1444, -1447 to -1456, -1458 and -1461. Fatty infiltration of only exocrine elements and moderate hyperplasia of the endocrine elements were seen in all guinea pigs excluding the ones given above.

Adrenal: Yellow granular pigment in the cytoplasm of the cortical epithelium was seen in all guinea pigs. Focal mild mineralization of the cortical epithelium was seen in 76-1435 and 76-1455.

Urinary bladder: Mild focal hyperplasia of the transitional epithelium was seen in 76-1444. Mineralization of surface epithelial cells was seen in 76-1452, -1453, and -1462 to -1465.

2.2 Untreated guinea pigs

Path. Accs. No.: 76-1470 to 76-1508.

Gross pathology: Consolidation of lungs was seen in 76-1488, -1490, -1506. Small necrotic foci were seen in the livers of 76-1486, -1488, and -1491. A contracted kidney was seen in 76-1493. Necrotic fat (mass) was found attached to mesentery of 76-1475 (3.57 gm), -1477 (3 x 2 cm), -1480 (4.5 x 2.5 cm), -1486 (1.0 x 2.0 cm), -1494 (1 x 2 cm), -1495, and -1496.

Histopathology:

Lungs: The presence of eosinophilic fluid exudate with cellular debris and the lymphoid aggregation in all guinea pigs was the same as seen in 2.1. The interstitium of all the lungs contained lesser number of macrophages than those seen in 2.1. The cytoplasm of these macrophages was granular and eosinophilic. Plant material with or without inflammatory infiltrates was seen in 76-1488 and -1490. Bone formation in the alveolar region was seen in -1474, -1475, -1476, -1478, -1490, -1493, -1499, -1501, and -1506. Focal consolidation of all lungs was seen.

Liver: Fatty infiltration (mild) of hepatocytes was seen in 76-1472 and 76-1478. Moderate hyperplasia of bile ducts was seen in 76-1474. A myeloliposarcoma was seen in the liver of 76-1470.

Spleen: Macrophages with yellow granular material in the cytoplasm were seen in all guinea pigs.

Kidney: Multifocal mild to moderate mineralization of tubular epithelium was seen in 76-1470, -1471, -1473 to -1483, -1487 to -1508.

Pancreas: Fatty infiltration of exocrine and endocrine elements was seen in 76-1470 to -1475, -1478, -1480, -1482, -1486, -1488, -1490, -1492, -1494, -1495 to -1497, -1501, -1502, -1503, and -1507. The pancreas from the remaining guinea pigs showed fatty infiltration of exocrine elements and hyperplasia of endocrine elements.

Adrenal: Yellow granular pigment in the cytoplasm of the epithelium of the cortex of all guinea pigs was seen.

Urinary bladder: Mineralization of the surface epithelium was seen in 76-1472, -1475, -1480, -1495, -1497, -1498, and -1504. Subacute cystitis was seen in 76-1470 and 76-1494.

Mesenteric masses: 76-1473: Granuloma of mesenteric fat. Entrapped pancreatic exocrine elements were present.
76-1475: Granuloma of mesenteric fat.
76-1477: Thrombosis of veins with degenerative fat.
76-1480: Thrombosis of veins and degenerating fat.
76-1486: Granuloma of mesenteric fat; polarising yellow material seen.
76-1494: Degenerating fat.
76-1496: Granuloma of mesenteric fat.

Comment: For comparison, this comment shall include rat and guinea pig data. Both the rats and the guinea pigs exposed to PVC by inhalation exhibited the presence of PVC particulates in the pulmonary macrophages, although the pattern of macrophage accumulation between the two species differed. There was no inflammatory or any other deleterious effect seen in the lungs of these animals that could be attributable to PVC inhalation.

The incidence of perivascular lymphoid aggregations in the lungs of guinea pigs was similar in both exposed and controls. The presence of bony spicules in the lungs of exposed and control guinea pigs was observed. The pathogenesis of these two conditions is not known (Thompson, S. W., Hunt, R. D. et al: Am. J. Path. 40:507-517 (1962); Kaufman, A. F.: Lab. Anim. Care 20:1002-1003 (1970)) and is worth exploring as NIOSH uses guinea pigs as one species of animals in biological experiments. The nephrocalcinosis seen in the exposed and control guinea pigs may be related to diet (J. C. Woodard: Am. J. Path. 65:253-268 (1971) and 65:269-278 (1971)). Corollary

to the above observation was the finding of invariable fatty infiltration of exocrine and endocrine elements of the pancreas in both the exposed and control guinea pigs and the hyperplasia of islets of Langerhans seen in both the rats and the guinea pigs employed in this experiment. In addition, the vascular wall calcification in the pulmonary vessels of rats is disturbing. All of these "incidental" findings strongly suggest that these animals had metabolic problems probably related to the animal diet. The changes seen in the testes of rats were non-specific and probably not related to treatment. The incidence of neoplasms in the adrenals of rats is within the normal range observed for Sprague-Dawley rats of this age.

Choudari Kommineni, D.V.M.

R&S 112900

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

TO : Chief, ETB
Through: Director, DBBS
Chief, BSB

DATE: September 6, 1978

FROM : Research Veterinary Medical Officer

SUBJECT: Pathology Report on Monkeys Exposed to Amorphous Silica-F

Ten male cynomolgus monkeys were exposed to silica-F at 15 mg/m^3 by inhalation for 6 hours/day, 5 days/week for almost 13 months. The control male monkeys (10) were maintained in an open animal room in their individual cages. The animals were killed within 48 hours after final exposure. At the time of autopsy, tissues from the lungs (all lobes with trachea), thyroid, heart, tracheobronchial lymph nodes (TBLN), mesenteric lymph nodes (MLN), liver, spleen, kidney, urinary bladder, prostate, testis, stomach (pylorus), duodenum, pancreas, adrenals, and skin from the abdomen were saved for histopathology evaluation.

1.1 Control Monkeys

Path. Accss. #77-2975, 77-2979, 77-2981, 77-2983 to 77-2986, 77-2991, 77-2993 and 77-2994.

Gross Pathology: Some or all lobes of the lungs were found adhering to the thoracic wall in all monkeys. TBLNs were black in 77-2984 to 77-2986. Nodules varying from 1 mm to 8 mm in diameter were seen on the spleens of 77-2979, 77-2981, 77-2983 and 77-2993.

Histopathology:

Lungs: Aggregates (70 to 400μ in diameter of particles, lymphocytes and macrophages adjacent to medium-sized blood vessels and bronchioles were seen in all lungs. Occasionally, they were present in alveolar walls. The size and frequency of these aggregates varied considerably among monkeys. The least number of aggregates appeared in monkeys 77-2981, 77-2983, 77-2985 and 77-2993. Approximately 1-7 were present/section. The 77-2975, 77-2979, 77-2986 and 77-2991 had greater numbers of these aggregates (5-15/section) and some of these were larger. The largest number of and the largest sized aggregates, as many as 11, were seen in one microscopic field at 25X magnification in 77-2994. The aggregates were principally composed of particles and macrophages. The particles were black, brown, acicular, fibrous and/or granular. The

particles were either intracellular (macrophages) or extracellular. Many of the particles in most sections were birefringent and in 77-2994 most of the particles were birefringent. The frequency, size and composition of lesions in 77-2984 were intermediate between those seen in 77-2994 and the other monkeys. Collagen was present in some of the aggregates in lungs from 77-2984 and 77-2994 but not in the other lungs.

Smooth muscle hyperplasia around arteries, some alveolar ducts and respiratory bronchioles was seen in 77-2979 (1+), 77-2981 (2+), 77-2983 (1+), 77-2985 (1+), 77-2986 (3+) and 77-2991 (2+). The numbers in the parentheses above indicate the degree of smooth muscle hyperplasia. Pulmonary nematodiasis (strongylidosis) was seen in 77-2979, 77-2984 and 77-2985. A granuloma of undetermined parasitic origin (Verminous pneumonia) was also seen in the lungs of 77-2984. Focal squamous metaplasia of some alveoli with mixed cell infiltrate was also present in the lungs of 77-2985. Multiple gaint cells with plant material were seen in the lungs of 77-2991. All monkeys exhibited segmental, medial, hypertrophic, non-inflammatory arteriopathy in medium-sized arteries.

TBLNs: All monkeys had macrophage accumulations (sheet-like) replacing the medulla of the lymph nodes. The degree of deposition of macrophages with particulate material varied from 50% to 10% replacement of the lymph node. These macrophages contained particulate material similar in every aspect to that seen in the lung macrophages. The particle retention in the lymph nodes must have rendered the TBLNs dark as seen grossly.

Liver: A calcified parasitic granuloma was seen in 77-2986. Diffuse, intense fatty infiltration of the hepatocytes was seen in 77-2994.

MLN: Depleted medulla and follicular hyperplasia were seen in all monkeys.

Adrenal: A peri-adrenal parasitic granuloma was seen in 77-2979.

The other tissues examined were unremarkable.

1.2 Monkeys Exposed to Silica-F

Path. Accss. #77-382, 77-2318 to 77-2326.

Gross Pathology: Adhesions between the lungs and the thoracic wall were seen in 77-2318, 77-2319, 77-2324 and 77-2326.

Histopathology:

Lungs: Macrophage accumulations with pigmented anisotropic particles similar to those seen in the controls were seen in all lungs. The distribution of the macrophages and the degree of deposition of the particles were the same as in Controls 1.1. In addition to these macrophage clusters were more macrophages containing fine granular to amorphous material (non-birefringent), as seen with phase contrast (blue to blue-black), that differed from the above particulates. The macrophage accumulations formed macules (170-600μ in diameter) around blood vessels (arteries and veins), in alveoli, alveolar ducts and secondary bronchioles. The macules around blood vessels did not impinge on the integrity of the vascular lumens or walls. However, the macules in the alveolar areas and alveolar ducts (300 to 600μ in diameter) obliterated or partially blocked the acini. The macules close to the secondary bronchioles disrupted the smooth muscle wall and, in some instances, pushed the lining epithelium into polypoidal projections, thus reducing the lumens of the airways. All the above morphologic alterations would probably have some effect on pulmonary physiology. In addition, these macrophage macules contained very fine bands of connective tissue traversing the macules and sometimes surrounding them. These fine connective tissue bands seemed to serve as scaffolding to these macules. Some macules had the particulate materials (black) as seen in the controls. Most of the macules were discrete with occasional coalescence with the neighboring macules seen. The degree of macrophage accumulation was 3/4 less in 77-2322 than the other treated primates. A total of 94 macules, most of them being 400 to 600μ in diameter, were seen at 25X magnification in most of the monkeys, thus replacing 25 to 30% of the lung parenchyma. The arteriopathy seen in controls was also present in all the monkeys in this group. In addition, the lungs of 77-2326 showed focal arteritis. Pulmonary nematodiasis was seen in 77-2321 and 77-2326.

TBLN: The macrophage accumulations (sheet-like) with similar particles (grey, brown and black) as in the controls were present in the medulla. In addition, more macrophages with amorphous to fine granular material (blue) that was isotropic were present in the medulla.

Heart: Intramural nematode was present in 77-2326.

MLN: Similar to the controls.

Kidney: Focal gaint cells (Syncitial) were seen in the collecting tubules of 77-2320. Focal mild calcification of collecting tubules was seen in 77-2321.
Testis: Calcification of some semeniferous tubules was present in 77-2321 and 77-2323.
The other tissues examined were unremarkable.

Comment: We have brought to the attention of the NIOSH staff the presence of particles in the lungs and the tracheobronchial lymph nodes of the control and treated monkeys used in the coal dust inhalation experiments. We stated that "these particles exhibited a very low degree of birefringence. Such birefringent particles may be of silaceous or quartz material. Most likely the silicates are the dominant ones. The monkeys used in the current experiment carry the same type of particles. The Silica-F monkeys were exposed to high concentrations of amorphous silica (15 mg/m^3). This induced the macrophage accumulations in the lungs and the attendant morphologic changes. The presence of meagre connective tissue in these monkeys' lung macules should be noted. This is substantiated by the hydroxyproline values (Mr. Dennis Lynch provided the data) obtained from the serum and the lung tissue of these monkeys. However, the abundance of macules containing fine bands of connective tissue is significant in view of previous reports that "amorphous silica" is innocuous.

The macrophage macules probably altered the physiology of the lungs with regard to the pulmonary respiratory functions. It is possible that these macules would resolve in time if the insult was abated. The respiratory functions may even partially improve. As the monkeys were killed immediately after exposure was stopped, this aspect remains to be studied. The translocation of the Silica-F was confined to the tracheobronchial lymph nodes as was the case with particles seen in the controls.

The presence of the nematode parasites and other unidentified parasites in both the controls and the Silica-F treated monkeys should be noted. NIOSH being a part of CDC and DHEW, I am hopeful that precautionary measures to prevent occurrences of both zoonotic and anthropogenic diseases are followed. If such were not in force, I urge immediate institution and scrupulous adherence of the appropriate precautionary measures to avoid any problems.

Cursory look at the differential white blood cell counts did not show any eosinophilia in 7--2984, 77-2979 and 77-2985 which is disturbing. On gross examination the 77-2979 was found to have "worm nodule" in the large intestine. We looked for this in the fixed tissues but were unable to find the large intestine with "worm nodule."

The synergistic or antagonistic effects of particulates containing silica on this study should be a cause for concern.

Choudari Kommineni, D.V.M., Ph.D.

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

TO : Chief, ETB
Through: Director, DBBS
Chief, BSB

DATE: September 6, 1978

FROM : Research Veterinary Medical Officer

SUBJECT: Pathology Report on Monkeys Exposed to PVC

Ten male Cynomolgus monkeys were exposed to PVC at 10 mg/m^3 by inhalation for 6 hours/day, 5 days/week for almost 22 months. Control male monkeys (10) were maintained in an open animal room in their individual cages. The monkeys were killed within 48 hours after the final exposure. At the time of autopsy, tissues from the lungs (all lobes with trachea), thyroid, heart, tracheobronchial lymph nodes (TBLN), mesenteric lymph nodes (MLN), liver, spleen, kidney, urinary bladder, prostate, testis, stomach (pylorus), duodenum, pancreas, adrenals, and skin from the abdomen were saved for histopathology.

1.1 Control Monkeys
Path. Accss. #77-2975, 77-2979, 77-2981, 77-2983 to 77-2986, 77-2991, 77-2993 and 77-2994.
Gross and histopathology: See the pathology report on monkeys exposed to Silica-F.

1.2 Monkeys Exposed to PVC
Path. Accss. #77-2974, 77-2976, 77-2980, 77-2982, 77-2988, 77-2989, 77-2995, 77-2996, 77-2997 and 77-2999.
Gross Pathology: Adhesions between the lobes of the lung and the thoracic wall were seen in 77-2980, 77-2995 and 77-2997. Multiple black areas were seen in the lungs of 77-2976, 77-2980, 77-2982, 77-2988, 77-2989, 77-2996, 77-2997 and 77-2999. Enlarged and black MLNs were seen in 77-2974 and 77-2976.
Histopathology:
Lung: Macrophages with anisotropic particles as in the controls were similarly present in all these monkeys. Admixed with these macrophages were other macrophages with spherical material (PVC) of varying size in the cytoplasm. About 15% of the total macrophage aggregates (macules) in 77-2997, 77-2988 and 77-2980 contained black to brown anisotropic particles of the same degree of deposition as in the controls. In the rest of the PVC exposed monkeys 20 to 22% of

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non-specific one, inasmuch as these materials (PVC and amorphous silicas-F, G and P) show diverse chemical composition. The second paragraph under "Comment" in the pathology report on monkeys exposed to amorphous silica-F also applies here. The influence of the brown and black particles on the biologic effects of PVC are hard to define but should be carefully considered. The only contribution of the inhaled PVC dust deposition and retention to pulmonary tissue morphology was numerous aggregations of PVC-containing macrophages.

Choudari Kommineni, Ph.D., DVM

IMPERIAL CHEMICAL INDUSTRIES LIMITED
PLASTICS DIVISION—WELWYN GARDEN CITY

From: J STAFFORD
Division Manager
Health & Environment Protection
DSO-16
Ext 3162/3859/2096
3859 - Dr Stafford's Sec.
2096 - Telephone contact in TS

To:

Dr G Pigott
Dr W G F Adams
Dr B Bennett
Dr F W Best
Dr D P Duffield
Mr G J Sleddon
Dr D M Ferguson
Mr M J S Gibbons
Mr D Ryerson
Dr T R Torkelson
Mr J Lawrence
Mr J Seawell
Dr M N Johnson
Mr P Claus
Dr J G Kammuller
Mr J C Thomas
Dr R Mattiussi
Dr J P Tassignon

PVC DUST

You may care to see Dr Adams' comments on the Trent Lewis letter of 17/3 which I circulated to you on 6 May.

J Stafford

JS/SEW/DSO-16
20/5/80

R&S 112907

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Chemical Industries Limited

Plastics Division

From W G F Adams
Division Medical Officer

To Dr J Stafford
Division Manager
Health & Environment Protection

Copies to

Your ref.	Our ref	Tel ext	Date
JS/SEW	WGFA/AGL/F11	3039	12 May 1980

PVC DUST - TRENT LEWIS LETTER

Thank you for letting me see a copy of this letter to you. There are one or two points worth making.

Although a drop in FEV1 and FVC does indicate chronic obstructive lung disease, I do not think that even the IOM would make such a claim for the population studied by them on the findings of their report. They should be in a stronger position to give a clinical opinion following the next survey when they are, as you know, looking at the men with X-ray changes. The possibility that the narrowing of the airways is due to the physical deposition of dust is an interesting hypothesis. I do find it rather difficult to conceive of such a neat arrangement, but shall ask Dr Seaton for his opinion on this as, presumably, other dusts would have a similar effect.

Finally, it is rather disturbing to see that even an expert has apparently misread the report and is under the impression that concentrations of 2 mg/m^3 could cause the effects reported. The message that historically exposures were much greater does not appear to have got home.

I have not copied this letter to the circulation on yours but have no objection to this being done if you wish.

W G F Adams

Registered in England No. 218019 Registered Office - Imperial Chemical House, Millbank, London SW1P 3JF

IMPERIAL CHEMICAL INDUSTRIES LIMITED
PLASTICS DIVISION—WELWYN GARDEN CITY

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PVC DUST - TRENT LEWIS LETTER OF 17 MARCH 1980

To complete your file on this subject and further to my note of 20 May, you may care to have a copy of Dr Seaton's letter of 20 May commenting on Dr Trent Lewis' letter of 17 March 1980.

J Stafford

JS/SEW/DSO-16
11 June 1980

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Imperial Chemical Industries Limited

Plastics Division

From W G F Adams
Division Medical Officer

To Dr J Stafford
Division Manager
Health & Environment Protection

Copies to

Your ref.	Our ref	Tel ext	Date
	WGFA/AGL/F11	3039	28 May 1980

I enclose a copy of Anthony Seaton's reply to my query about Trent Lewis's letter. As you see, he states in rather more detail what I said in my letter to you and disposes of the somewhat quaint notion that obstructive airway disease could be due to physical deposition of PVC in the smaller airways.

W G F Adams

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Roxburgh Place
Edinburgh
EH8 9SU
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Institute of Occupational Medicine

Our ref D.222
Your ref

20 MAY 1980

14th May 1980

Dr. W.G.F. Adams,
Division Medical Officer,
Imperial Chemical Industries Ltd.,
P.O. Box No. 6,
Bessemer Road,
WELWYN GARDEN CITY,
Herts.

Dear Bill,

Thank you for showing me the letter from Trent Lewis to John Stafford. I found this letter confused and I think the explanation of this is that Mr. Lewis is unfamiliar with the medical implications of the terms 'chronic obstructive lung disease' and 'pneumoconiosis'. For example, he says that our study indicates that PVC dust exposure leads primarily to chronic obstructive lung disease. This is not a conclusion that can be drawn from our study without defining what is meant by chronic obstructive lung disease. There certainly was no apparent relationship to the syndrome of cough and sputum production though there was a relationship between estimates of dust exposure and reduction in FEV_1. At the same time there was a reduction in forced vital capacity which is far from typical of what most people understand by chronic obstructive lung disease. I doubt if a PhD toxicologist could be expected to understand the niceties of these physiological and epidemiological findings. Secondly, he talks about a classical pneumoconiotic disease syndrome without saying what he means by that. There is, of course, no such classical syndrome. Pneumoconiosis, again to most people, means deposition in the lung of dust and the lung's reaction to it. Many different types have been described, notably mineral and organic pneumoconioses and of the mineral pneumoconioses there is a range from the most benign, such as stannosis to aggressive fibrotic syndromes, such as acute silicosis and asbestosis. The pathological range of such pneumoconioses is enormous from an inflammatory granulomatous process in acute farmers' lung to fibrosis to an acute pulmonary oedema type syndrome in acute silicosis. Description of a classical pneumoconiosis must include attribution of that pneumoconiosis

to its cause, for example, classical silicosis, classical coalworkers' pneumoconiosis and so on.

Having said this, my concept of what is happening, which as you know is not based on any pathological studies as yet, is that a lesion is developing, capable of causing obstruction to airflow and some restriction of lung volumes, in association with small round shadows on the chest X-ray. From our studies this does not appear to be a progressive lesion nor does it usually appear to cause any serious pulmonary impairment. It seems likely, therefore, that it is an inflammatory or possibly granulomatous process occurring in the smaller airways, for example, the terminal and respiratory bronchioles. This, however, must remain a speculation until more work on the human pathology has been carried out. I do regard this as being a relatively urgent matter and I have arranged to meet with Chris Wagner and Dr. Harry in Blackpool on Wednesday, 11th June. I hope that you will be able to come along to this meeting as well.

Kind regards,

Yours sincerely,

Anthony Seaton,
Director.