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From J Stafford
Division Manager
Health, Safety & Environment Protection

Plastics
Division

To **DEC 07 1978**
See Circulation Below
R. N. WHEELER, JR.

Copies to

TO: SPI VINYL SUBCOMMITTEE

FROM: W D Davis/R N Wheeler
November 28, 1978

Your ref.	Our ref.	Tel ext.	Date
	JS/AMB/DSO-107	3162	17 October 1978

PVC DUST

You may care to see the attached letter and NIOSH report I have received from Dr Douglas of EMAS. This report seems reassuring but I would welcome the opinion of our Medical Committee who have been considering how to design a good PVC dust inhalation study. Has the need for such a study disappeared as a result of the NIOSH work? Dr M N Johnson of B F Goodrich, when he saw us on 9 October, knew of these results but was critical that the rodent species were sacrificed at 12 months (monkeys 22 months). Dr Johnson thought that a well conducted full life study on PVC dust inhalation should still be considered and the possibility of Transatlantic cooperation explored to derive both protocol and funding.

Circulation

Dr W G F Adams
Dr D P Duffield
Dr G Pigott
Dr B W Duck
Dr M Sharratt
Dr P Grasso
Dr J T Carter
Dr D W Flester
Dr G Paddle
Dr K S Williamson
Dr I F H Purchase
Sir C Lawrence Jones
Dr F W Best
Mr G J Sleddon
Mr W Adams
Mr R Hards
Mr P E M Sharrock
Mr T L Phillips
Mr B N P Hutcheson
Mr H M Clayton

Mr T W Moffitt
Dr L de Boer
Dr J G Kammuller
Mr J C Thomas
Mr M Bonnefoy
Dr T Garlanda
Dr M N Johnson
Dr T R Torkelson
Mr R N Wheeler (Jr)
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Dr R E Davies, ICI Melbourne
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Chief Medical Officer, ANCI

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Dr J Stafford
Division Manager
Health & Environment Protection
ICI Limited, Plastics Division
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Bessemer Road
Welwyn Garden City AL7 1HD

Your reference

Our reference
1/MS/406/225/78

Date
6 October 1978

Dear Dr *John* Stafford

PVC DUST

Thank you for sending me a copy of Maxweiler's report on PVC dust and the item from Tox-Tips. Both will be discussed at the next tri-partite medical meeting which should take place in late November. Dr Elliott Harris the head of the Division of Bio-Medical and Behavioural Science, NIOSH, was here on Tuesday 3 October and told me that the study by Dr Trent Lewis had been completed and no evidence of carcinogenicity or pneumoconiosis had ... been found in any of the animal species. I enclose copies of the reports given to me by Dr Harris.

Yours sincerely

D B Douglas
Deputy Director of Medical Services

cc: Dr R Owen
Dr P S Fairweather

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PVC Chronic Inhalation Toxicology Study

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/m³ 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.	CI 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	4.65-9.25	28,180	30,510 ^{10,414}
Guinea Pig	40	40	379	245	1428	10.6	-	14,700	14,698 ^{15,124}
Rat	80	80	376	244	1424	10.6	-	14,640	14,627 ^{15,044}

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

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 $0.2'' \text{H}_2\text{O}$. 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 $10 \text{ mg}/\text{m}^3$ 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

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DATE: May 5, 1977

D. G. M. 23

SUBJECT: Pathology Report on Rats Exposed to PVC

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.

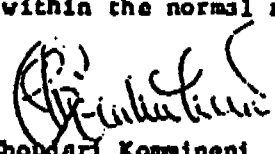
Pancreas: Mild hyperplasia of endocrine elements was seen in 76-1395 to -1399, -1402, -1404 to -1410, -1414 to -1418, -1420, -1421, -1424 to -1426, -1428, -1429, -1510, -1511, -1514, -1515, -1518 to -1523, -1532, -1539 to -1542, and -1545.

- 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.
- Mes:** 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); Kaufmann, 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.


Choudhary 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, ETS
Through: Director, DBBS
Chief, BSB *QJW*

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/m³ 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. Access. #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. Access. #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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the macules had these black to brown particles. A total of 110 macrophage aggregates were seen at 25X magnification in most of the lungs. The diameter of many of these aggregates varied from 100 to 200 μ while the largest, present in the alveolar region, measured 475 μ . The macrophage aggregates were present in the alveolar walls, alveoli, partially obstructing the alveolar lumens. They were also present around tertiary bronchioles and in some alveolar ducts without causing observable obstruction. A few places showed submucosal accumulations with no polypoidal projections. With phase contrast illumination these macrophage accumulations appear as blue aggregates. This tinctorial character is distinct from the macrophage aggregates seen in amorphous silica (F, G and P) exposed monkeys.

Focal hyperplasia of type II cells was present in 77-2989. Smooth muscle hyperplasia was seen around blood vessels and alveolar walls in 77-2996. Acute bronchopneumonia was seen in 77-2988. Plant material was present in a bronchus in 77-2999. Multiple giant cells away from the plant material were seen in the 77-2999. Non-inflammatory arteriopathy as in the controls was present in all these monkeys.

TBLN: As in the controls the medulla contained macrophages with anisotropic particles. In addition, other macrophages with cytoplasmic material (PVC - blue in color - see lung) were present. Together, these macrophages replaced most of the medulla of the TBLNs in all monkeys.

Liver: Diffuse fatty infiltration of the hepatocytes was present in 77-2982 and 77-2996.

Kidney: Multifocal calcification of cortical tubules was seen in 77-2995.

MLN: See the controls.

The other tissues examined were unremarkable.

Comment: A slightly higher number of macrophage aggregates containing black and brown birefringent particles were seen in PVC exposed than in the control monkeys. The pattern of distribution of the macrophage accumulations in the PVC exposed and the amorphous silica (F, G and P) exposed monkey lungs and the TBLNs was similar. The macules were smaller in size in PVC exposed than those seen in the amorphous silica (F, G and P) exposed monkeys. The monkey lung reaction suggests that it may be a

Chief, ETS

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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

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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

v. j. ...

(24)

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/m³, 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/m³ 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 lumen. 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:

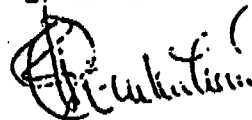
Lungs: The presence of eosinophilic fluid exudate with cellular debris and the lymphoid aggregation in all guinea pigs was the same as seen in 2.1. The interstitium of all the lungs contained lesser number of macrophages than those seen in 2.1. The cytoplasm of these macrophages was granular and eosinophilic. 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 myel liposarcoma 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.

PLASTICS DIVISION

NOTE ON A TELEPHONE CONVERSATION WITH DR M N JOHNSON OF BF GOODRICH,
20 OCTOBER 1978

PVC DUST - NIOSH STUDIES

Dr Johnson 'phoned to say he had now had a talk with Dr Trent Lewis of NIOSH on the 3 mammal study. Dr Lewis emphasized that this was in n sense a carcinogenicity study. It was a study aimed at ascertaining about pulmonary function and fibrosis. Dr Lewis was happy with th outcome of the work in that nothing happened and there was nothing to comment on the subject of pulmonary function and fibrosis. He thought the study was totally unsuited to gauge carcinogenicity.

In Dr Lewis's view an inhalation study of PVC dust on animals to demonstrate carcinogenicity is a very difficult undertaking. He would be very unwilling to tackle it unless there was something equivocal in the epidemiology that needed to be resolved. Even then he would advocate expanding the epidemiology to get a more positive answer. If there is a positive answer from the epidemiology no amount of animal work would make any difference and again he stressed that dust inhalation tests for carcinogenicity on animals are long, tedious, difficult and uncertain.

J Stafford
Division Manager
Health & Environment Protection

JS/MJE/DSO-107
23 October 1978

RECEIVED
JUN 1 1978
F. N. WILKINSON, JR.

Circulation

Dr W G F Adams
Dr D P Duffield
Dr G Pigott
Dr B W Duck
Dr M Sherratt
Dr P Grasso
Dr J T Carter
Dr D W Plester
Dr G Paddle
Dr K S Williamson
Dr I F H Purchase
Sir C Lawrence-Jones
Dr F W Best
Mr G J Sleddon
Mr W Adams
Mr R Hards
Mr P H M Sharr ck

Mr T L Phillips
Mr B N P Hutchesson
Mr H M Clayton
Mr T W Moffitt
Dr L de Boer
Dr J G Kammuller
Mr J C Thomas
Mr M Bonnefoy
Dr T Garlanda
Dr M N Johnson
Dr T R Torkelson
Mr R N Wheeler (Jr)
JS (2)

Dr R E Davies, ICI Australia
Mr K H Whit , Duperial SAIC
Chi f Medical Officer, AECI

UCC
010759

Box No 6
Dassam Road
Wetwyn Garden City Hertfordshire AL7 1HD

Telephone: Wetwyn Garden 23400 (STD Code 07073)
Telex 264291

RECEIVED

OCT 27 1978

R. N. WHEELER, JR.



Imperial
Chemical
Industries
Limited

From J Stafford
Division Manager
Health, Safety and Environment Protection

Plastics
Division

To
DEC 07 1978
See Circulation Below
R. N. WHEELER, JR.

Copies to

TO: SPI VINYL SUBCOMMITTEE

FROM: W D Davis/R N Wheeler
November 28, 1978

Your ref.	Our ref.	Tel ext	Date
	JS/AMB/DSO-107	3162	17 October 1978

PVC DUST

You may care to see the attached letter and NIOSH report I have received from Dr Douglas of EMAS. This report seems reassuring but I would welcome the opinion of our Medical Committee who have been considering how to design a good PVC dust inhalation study. Has the need for such a study disappeared as a result of the NIOSH work? Dr M N Johnson of B F Goodrich, when he saw us on 9 October, knew of these results but was critical that the rodent species were sacrificed at 12 months (monkeys 22 months). Dr Johnson thought that a well conducted full life study on PVC dust inhalation should still be considered and the possibility of Transatlantic cooperation explored to derive both protocol and funding.

Circulation

Mr W G F Adams
Dr D P Duffield
Dr G Pigott
Dr B W Duck
Dr M Sharratt
Dr P Grasso
Dr J T Carter
Dr D W Flester
Dr G Paddle
Dr K S Williamson
Dr I F H Purchase
Sir C Lawrence Jones
Dr F W Best
Mr G J Sleddon
Mr V Adams
Mr R Hards
Mr P E M Sharrock
Mr T L Phillips
Mr B N P Hutchesson
Mr H M Clayton

Mr T W Moffitt
Dr L de Boer
Dr J G Kammuller
Mr J C Thomas
Mr M Bonnefoy
Dr T Garlanda
Dr M N Johnson
Dr T R Torkelson
R N Wheeler (Jr)
JS (2)

Dr R E Davies, ICI Melbourne
Mr K H White, Duperial SAIC
Chief Medical Officer, AECI



**Health &
Safety
Executive**

Baynards House
1 Chepstow Place
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Dr J Stafford
Division Manager
Health & Environment Protection
ICI Limited, Plastics Division
P O Box No 6
Bessemer Road
Welwyn Garden City AL7 1HD

Your reference

Our reference
1/MS/406/225/78

Date
6 October 1978

Dear Dr *John* Stafford

PVC DUST

Thank you for sending me a copy of Waxweiler's report on PVC dust and the item from Tox-Tips. Both will be discussed at the next tri-partite medical meeting which should take place in late November. Dr Elliott Harris the head of the Division of Bio-Medical and Behavioural Science, NIOSH, was here on Tuesday 3 October and told me that the study by Dr Trent Lewis had been completed and no evidence of carcinogenicity or pneumoconiosis had ... been found in any of the animal species. I enclose copies of the reports given to me by Dr Harris.

Yours sincerely

D B Douglas
Deputy Director of Medical Services

cc: Dr R Owen
Dr F S Fairweather

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PVC Chronic Inhalation Toxicology Study

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'73 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/m³ 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	4.65-9.25	28,180	30,510 ^{14,417}
Guinea Pig	40	40	379	245	1428	10.6	-	14,700	14,698 ^{14,144}
Rat	80	80	376	244	1424	10.6	-	14,640	14,627 ^{15,044}

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

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" H₂O. 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/m³ 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

TO : Chief, NSB
THROUGH: Chief, Pathology Section

DATE: May 5, 1977

D. G. H. 23

FROM : Veterinary Pathologist, Pathology Section

SUBJECT: Pathology Report on Rats Exposed to PVC

Male rats were exposed by inhalation to polyvinyl chloride (PVC), respirable concentration 10 mg/m³, 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/m³ 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 stelectasis) 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 76-1353, -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.
- Mammary:** 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. P.: 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.


Choudhary Kommaneni, 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, ETB
Through: Director, DBBS
Chief, BSB *[Signature]*

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/m³ 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. Access. 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. Access. 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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the macules had these black to brown particles. A total of 110 macrophage aggregates were seen at 25X magnification in most of the lungs. The diameter of many of these aggregates varied from 100 to 200 μ while the largest, present in the alveolar region, measured 475 μ . The macrophage aggregates were present in the alveolar walls, alveoli, partially obstructing the alveolar lumens. They were also present around tertiary bronchioles and in some alveolar ducts without causing observable obstruction. A few places showed submucosal accumulations with no polypoidal projections. With phase contrast illumination these macrophage accumulations appear as blue aggregates. This tinctorial character is distinct from the macrophage aggregates seen in amorphous silica (F, G and P) exposed monkeys.

Focal hyperplasia of type II cells was present in 77-2989. Smooth muscle hyperplasia was seen around blood vessels and alveolar walls in 77-2996. Acute bronchopneumonia was seen in 77-2988. Plant material was present in a bronchus in 77-2999. Multiple giant cells away from the plant material were seen in the 77-2999. Non-inflammatory arteriopathy as in the controls was present in all these monkeys.

TBLN: As in the controls the medulla contained macrophages with anisotropic particles. In addition, other macrophages with cytoplasmic material (PVC - blue in color - see lung) were present. Together, these macrophages replaced most of the medulla of the TBLNs in all monkeys.

Liver: Diffuse fatty infiltration of the hepatocytes was present in 77-2982 and 77-2996.

Kidney: Multifocal calcification of cortical tubules was seen in 77-2995.

MLN: See the controls.

The other tissues examined were unremarkable.

Comment: A slightly higher number of macrophage aggregates containing black and brown birefringent particles were seen in PVC exposed than in the control monkeys. The pattern of distribution of the macrophage accumulations in the PVC exposed and the amorphous silica (F, G and P) exposed monkey lungs and the TBLNs was similar. The macules were smaller in size in PVC exposed than those seen in the amorphous silica (F, G and P) exposed monkeys. The monkey lung reaction suggests that it may be a

Chief, ETB

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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

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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)

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/m³, 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/m³ 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, -1439, 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 spiculus) 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); Kaufmann, 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

t the above observati n was the finding f invariable fatty infiltration of exocrine and endocrine elements f the pancreas in both the exposed and control guinea pigs and the hyperplasia f islets f Langerhans seen in both the rats and the guinea pigs empl yed in this experiment. In addition, the vascular wall calcification in the pulmonary vessels f 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
Choudari Kommineni, D.V.M.

NOTE ON A TELEPHONE CONVERSATION WITH DR M N JOHNSON OF BF GOODRICH,
20 OCTOBER 1978

PVC DUST - NIOSH STUDIES

Dr Johnson 'phoned to say he had now had a talk with Dr Trent Lewis of NIOSH on the 3 mammal study. Dr Lewis emphasised that this was in a sense a carcinogenicity study. It was a study aimed at ascertaining about pulmonary function and fibrosis. Dr Lewis was happy with the outcome of the work in that nothing happened and there was nothing to comment on the subject of pulmonary function and fibrosis. He thought the study was totally unsuited to gauge carcinogenicity.

In Dr Lewis's view an inhalation study of PVC dust on animals to demonstrate carcinogenicity is a very difficult undertaking. He would be very unwilling to tackle it unless there was something equivocal in the epidemiology that needed to be resolved. Even then he would advocate expanding the epidemiology to get a more positive answer. If there is a positive answer from the epidemiology no amount of animal work would make any difference and again he stressed that dust inhalation tests for carcinogenicity on animals are long, tedious, difficult and uncertain.

J Stafford
Division Manager
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