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Dear Ted

PVC DUST

You may already have a copy of this paper. However, I remember that the last time we got any information about this work it came from Trent Lewis to our Government, to us and eventually back to American industry. I know we all heard Groth give this paper in March 1980 but just in case I am sending you a copy for your file.

The paper did remind me that it is now a long time ago since we had that famous Symposium in Bethesda. We knew at the time that it was a bit of a non-event but I had expected to find the papers published by this time. Obviously NIOSH and the other agencies have had other priorities imposed on them since that time!

With best wishes.

Yours sincerely

J Stafford
Health & Environment Protection

Prot. N. 1386

PNEUMOCONIOSIS IN ANIMALS EXPOSED TO POLYVINYL CHLORIDE DUST

Cit
First Issue
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4 1, 73-82
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ABSTRACT

Rats, guinea pigs and monkeys were exposed by inhalation (6 hours/day, 5 days/week) for up to 22 months to a 10 mg/m^3 concentration of PVC dust. Autopsies on rats and guinea pigs were performed after 12 months of exposure and on monkeys after 22 months of exposure. Lung function tests were performed on monkeys after 9, 14 and 22 months of exposure. Aggregates of alveolar macrophages containing PVC particles were found in the lungs of all animals. These aggregates were more numerous in the monkey lungs. No fibrosis or significant cellular infiltrates were present in or near these cellular aggregates. No significant effects on pulmonary function could be demonstrated in the monkeys exposed to PVC. Under the conditions of this experiment, inhaled PVC produced a benign pneumoconiosis.

INTRODUCTION

Approximately seven billion pounds of polyvinyl chloride (PVC) were produced in the United States in 1979. There are two major types of PVC production processes, suspension polymerization and emulsion polymerization. The latter process produces particles which are respirable and much smaller than those in the former process. These polymers of vinyl chloride are usually compounded with a variety of ingredients (e.g., plasticizers, light and heat stabilizers, pigments and fillers) and processed in several different ways to produce thousands of end products in common use in our society. About 40% of PVC is used to make sewage pipes, water pipes and conduits. It is also used to make construction siding, window sashes, electrical wire and cable insulation, packaging films (for meat, etc.), vinyl floor tile, wall coverings, phonograph records, shower curtains, bottles, fabrics for clothes, furniture, automotive parts and many other products.

Chest x-ray abnormalities, respiratory dysfunction and pulmonary granulomas have been reported in workers exposed to PVC dust during PVC manufacturing and fabrication (Tribukh, et al., 1949; Szende, et al., 1970; Vertkin and Mamoutov, 1970; Lilis, et al., 1975; Arnaud, et al., 1978; Mastrangelo, et al., 1979). Consequently, experimental studies were initiated in 1975 to study the effects of inhaled PVC dust in animals.

MATERIALS AND METHODS

Test Material

Ten pounds of PVC (trade name Geon 121) were obtained from Goodrich Chemical Company and used in this experiment. The manufacturer's specifications stated a particle size range of 0.5-1.5 µm. Electron microscopic examinations in this laboratory confirmed that at least 90% of the particles were less than 1.5 µm in diameter. The PVC was stored in its covered, fiber board shipping container throughout the duration of the study.

Dust Generation and Measurements

PVC powder was packed daily or every other day into a Wright dust feeder at a pressure of 3,000 lbs./in.^{2}. The generated dust was fed into the mainstream of the inhalation exposure chamber intake air supply and through a static eliminator before entering the 160 ft.^{3} chamber. Airflow through the chamber was maintained at 40 ft.^{3}/minute with a negative chamber pressure of 0.2 inches of water. Animals were exposed to PVC dust 6 hours per day, 5 days per week for up to 22½ months.

Four chamber dust samples were collected each day by drawing chamber environment air, at a rate of 10 liters/minute for 20 minutes, through DM 5 µm pore size metricel filters with a vacuum pump. In addition, simultaneous samples consisting of particles with an aerodynamic diameter $\leq$7 µm (respirable fraction) were collected with a 10-plate, horizontal elutriator. All samples were weighed immediately after each sampling period and the chamber dust concentrations calculated. Adjustments in the dust generating system after each sampling period were made when necessary to maintain a concentration approximating 10 mg of respirable

dust/m^3 of air. Daily and grand means (derived from averaging the daily means) for the total and respirable dust fractions were calculated.

Midway through the experiment two, six-hour chamber air samples were collected on charcoal tubes while PVC dust was being generated. Those two samples and the bulk PVC were analyzed for vinyl chloride by gas chromatography. Samples of dust that were allowed to settle on formvar-coated copper grids placed in the chamber during the PVC dust generation were examined by transmission electron microscopy.

Animals

Animals used in this study were male, Cesarean-derived, Sprague-Dawley rats (Laboratory Supply Company, Inc., Indianapolis, Indiana); male, Hartley guinea pigs (Sweetwater Farms, Hillsboro, Ohio); and imported, adult, male Cynomolgus monkeys (Primate Imports Corp., Long Island, New York). The treatment and control groups each contained 80 rats, 40 guinea pigs and 10 monkeys. Because of difficulties in obtaining imported monkeys from the supplier, the control group of monkeys was received several months before the exposed group of monkeys. They were not randomly assigned, because the control group was also used for the control group in another ongoing experiment. Consequently, at time of first exposure, the mean weight of the control monkeys was 4219 grams and that of the exposed group 3361 grams. In the ensuing 22½ months, the controls gained 552 grams in weight, whereas, the exposed group gained 2116 grams.

The rats and guinea pigs were quarantined for two weeks and the monkeys were quarantined for one month prior to the initiation of the inhalation exposures. Stainless and galvanized steel open wire mesh cages were used as exposure caging to provide adequate distribution of the dust aerosols within the exposure chambers. All of the animals in the study were individually marked by toe-clipping or tatoo. All three species were individually housed during the 6-hour exposures, whereas the rats and guinea pigs were housed two to four animals per cage at all other times. Control animals were housed in similar cages in separate animal quarters and exposed to filtered air 24 hours/day. The exposed animals were also housed in the animal quarters except during the 6-hour inhalation exposure. Rats, guinea pigs, and monkeys were fed standard laboratory pellet diets (Rodent Laboratory Chow, Guinea Pig Chow, and Monkey Chow-Jumbo from Ralston Purina, St. Louis, Missouri). Monkeys were given fresh fruit (oranges, bananas, or apples) twice a week. Tap water was available ad libitum except during the exposure period. Food was available to the rodents at all times except during exposure. The monkeys were fed once daily at the cessation of the exposure period.

Pathology

Within one day after the last exposure day, all the surviving rats and guinea pigs were autopsied. Their lungs were inflated with 10% buffered formalin and sections of liver, spleen, heart, kidney, pancreas, adrenals, thyroid, testis, and urinary bladder from each animal were fixed in 10% buffered formalin. Hematoxylin and eosin stained sections of each lobe of each lung and of each of the above tissues were prepared for and examined by light microscopy.

Within 48 hours of the last exposure day, all surviving monkeys were autopsied and sections of the same aforementioned tissues plus tracheobronchial and mesenteric lymph nodes, prostate, stomach, duodenum and skin were fixed and processed in the same manner as those for the rodents with the exceptions that two sections from each lobe of the lungs were examined, and some of the lung tissue was processed for examination by transmission electron microscopy.

Pulmonary Function

Before onset of exposures and after 9, 14 and 22½ months of exposure to PVC dust, the following pulmonary function tests were performed on fasted, anesthetized (pentobarbital anesthetic) exposed and control monkeys: total lung capacity (TLC), vital capacity (VC), inspiratory capacity (IC), residual volume (RV), forced expiratory volume in 0.5 seconds (FeV 0.5), peak expiratory flow (PEF), maximum expiratory flow volume (FEF) at 50%, 25% and 10% of vital capacity, resistance (RL), compliance (CL), closing volume (CV), N_2 washout (ΔN_2/100 ml) and volume of isoflow (VisoV). These tests were performed with a variable pressure, whole-body plethysmograph. Means and standard deviations for all parameters in each group were calculated at each interval and comparisons made between groups using parametric and non-parametric statistical analyses.

Results

The mean total dust concentration in the chambers for the rodents was 13.0 mg/m^3 (S.D. = 2.34) and for the monkeys 12.9 mg/m^3 (S.D. = 4.69). The mean respirable dust concentration was 10.4 mg/m^3 for both the rodents and the monkeys. The monkeys were exposed on 464 days for a total of 2818 hours while the rodents were exposed on 245 days for a total of 1426 hours.

The vinyl chloride concentrations in the chambers at the two sampling periods were 0.01 and 0.02 ppm. A small non-quantified amount of vinyl chloride was detected in the bulk PVC.

Electron micrographs of the settled chamber dust showed individual particles ranging from 0.13 to 1.68 μm in diameter and agglomerates measuring up to 12.8 μm in diameter. Although the agglomerates measuring greater than 7 μm in diameter accounted for only 2.3% (5/222) of all the particles counted, they were estimated to account for more than 20% of the mass.

Pulmonary Function

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 9 and 14) and were indicative of some small airway obstruction. At this time, however, these differences were not statistically significant (see Table 1). At the last evaluation (month 22) compared with baseline (preexposure) data, there were no significant differences for any parameter tested.

Because of the differences in animal sizes between the control and exposed groups for all except the 14 month interval, meaningful comparisons could be made only at that time period. At that time, the mean weight of the controls was 4470 grams and that of the exposed was 4190 grams. The results appear in Table 1. No statistically significant differences existed. Impairment of respiratory function does not appear to be indicated under the conditions of this study from exposure to respirable PVC dust.

Pathology

Ten exposed and 10 control monkeys were autopsied 22½ months after initiating exposures. No gross abnormalities were seen in the lungs or other organs that could be related to the exposures. Light microscopic examination of the lung sections of exposed animals revealed macrophage aggregates (Figures 1 and 2) in the alveolar walls, alveoli, alveolar ducts, respiratory bronchioles and around veins. The majority of the aggregates were 100-200 μm in diameter and some were as large as 475 μm in diameter. Their concentration varied from 3-7 per microscopic field at 100X magnification. The tightly packed, large, spherical macrophages contained colorless cytoplasm which appeared light blue under phase contrast microscopy. Only a rare aggregate contained any other type of infiltrating cells, which usually consisted of a few polymorphonuclear leukocytes. No other lesions that could be related to experimental treatment were present, and no metaplasia, interstitial fibrosis, nodular fibrosis or pneumonitis were present. The tracheobronchial lymph nodes contained aggregates of the same type of macrophages described above in the lungs. Transmission electron microscopic examination of the macrophage aggregates revealed numerous round particles that do not normally occur in macrophages and were of the same size and shape as PVC particles (Figure 3). Analysis of these particles with the microprobe revealed high concentrations of chlorine (Figures 4 and 5), thus, further establishing their identity as PVC particles. A few aggregates of birefringent particles appeared in the lungs and high concentrations in the lymph node of both the exposed and control monkeys. These particles were identified as mica, kaolin and quartz by the use of microprobe, electron and x-ray diffraction methods. The bulk PVC did not contain these minerals. No macrophage aggregates were present in the control monkey lungs. No treatment related lesions were seen in sections of the other organs examined.

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closely packed macrophages in the lesions shown by Arnaud, et al., the morphology of the lesion is similar to that seen in our exposed monkey lungs. Part of the compactness of the cells in their lesion could be explained on the basis of artifactual compression caused during the taking of the lung biopsy. No excess collagen was apparent in the light microscopic pictures of the granulomas they showed in their article, although they did refer to their case as a "case of discrete pulmonary fibrosis." Their electron microscopic pictures of the PVC particles in in vitro cell systems were very similar to what we saw in the macrophages in the monkey lungs. The PVC particles they showed in a macrophage from the lung biopsy appear to be clustered in lysosomes and the individual particles are not as dense as the ones we found in the monkey lungs. That difference might be related to the different exposure durations and differing intervals since last exposure. Their patient was exposed to PVC for 23 years (our monkeys were exposed for 22½ months) and had no PVC exposure for 6 years (our tissue was sampled within 48 hours of last exposure). It is possible that some of the ingredients in the PVC particles in the human lung were altered and leached out over a period of time.

Szende, et al. (1970), reported that the lung biopsy specimen from a worker who shoveled PVC for one year showed moderate diffuse fibrosis and contained a granuloma with concentrically arranged connective tissue fibers. We did not see this in the monkey lungs.

The apparent difference in response of the lung tissue from two workers exposed to PVC compared to the monkeys exposed to PVC might be related to a variety of factors, including differences in the PVC dusts. Since various types of

emulsifiers and initiators are used in making PVC, and since these are not completely removed from the powdered PVC, they might explain the differences observed. It would be prudent in the future to obtain more information on PVC manufacturing processes and content of PVC dusts when studying their health effects.

Mastrangelo, et al. (1979), published health findings on employees who were currently working in a PVC production factory. Twenty cases of pneumoconiosis were found in a population of 1216 workers. Although the data were not given, the authors stated that slight restrictive respiratory function impairments were associated with chest x-ray changes in a small percentage of cases. In our study, no differences in pulmonary function tests could be detected between exposed and control monkeys after 14 months of exposure to 13 mg PVC/m^3. Whether any pulmonary function deficits would have occurred upon further exposure cannot be ascertained from this study. The lack of any significant pulmonary function abnormality in these monkeys, however, does not mean that animals or humans exposed to other types of PVC dust or mixtures of PVC dust with vinyl chloride (or a multitude of other ingredients that might be used in fabricating PVC products) might not exhibit pulmonary function changes.

For the first time, we have been able to show that a PVC dust generated under controlled experimental conditions is respirable and is deposited in cell aggregates in the lungs of monkeys, that PVC particles within macrophages are fairly unique in appearance, and that their identity can be confirmed with microprobe analyses. No pulmonary function deficits were found after 14 months of exposure to PVC concentrations of 13 mg/m^3, thus, confirming the pathologi diagnosis of a benign pneumoconiosis.

ACKNOWLEDGMENTS

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FIGURES

Figure 1 - Macrophage aggregates in lung of monkey exposed to PVC dust for 22 months. Aggregates are primarily in respiratory bronchioles and alveolar ducts. (Original magnification on 35 mm film was 40x.)

Figure 2 - Macrophage aggregates in lung of monkey exposed to PVC dust for 22 months. (Original magnification on 35 mm film was 250x.)

Figure 3 - Transmission electron micrograph of a macrophage from the lung of a monkey exposed to PVC dust for 22 months. Note the numerous round and oval, electron dense particles comprising most of the cytoplasmic space. These are the inhaled PVC particles.

Figure 4 - Scanning electron micrograph of a 5 μm section of lung of monkey exposed to PVC dust for 22 months. This photo shows the numerous PVC particles which obscure the cellular outlines of the macrophages in which they are residing.

Figure 5 - Chlorine x-ray map of the same area and magnification depicted in Figure 4. The white dots indicate the presence of the element chlorine. Note that the dots are clustered in the same area as the PVC particles, thus confirming the identification of the PVC particles.

Figure 6 - Macrophage aggregates in the lung of a rat exposed to PVC dust for 12 months. Note vacuolated appearance of cells. (Original magnification on 35 mm film was 250x.)

TABLE 1. Results of Pulmonary Function Tests in Monkeys After 14 Months Exposure to PVC Dust*

Pulmonary Function Test	Groups	
	Control	Exposed
RL, $cmH_2O/L/sec$	12.1±4.0	13.8±3.9
CL, ml/cmH_2O	22.9±10	17.5±7.5
TLC, ml	357±39	360±75
VC, ml	334±36	339±73
IC, ml	185±19	210±58
RV, ml	40±10	36±11
RV/TLC, %	11.3±2	9.9±2
FeV 0.5/FVC, %	87.7±5.3	86.5±8.1
PF, ml/sec	943±91	960±139
FEF 50%, ml/s	920±91	905±138
FEF 25%, ml/s	648±173	655±235
FEF 10%, ml/s	262±114	269±134
CV, ml	21±9	21±11
ΔN_2/100 ml	1.05±0.3	0.67±0.4
Viso V, ml	28.7±19	19.9±14.3

*Data are presented as means ± one standard deviation for each of the parameters.

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WSJ 6/23/81

Nalco Chemical Unit Ex-Officials Charged With Faking Lab Data

Special to THE WALL STREET JOURNAL

CHICAGO—A federal grand jury indicted four former officials of Nalco Chemical Co.'s Industrial Bio-Test Laboratories Inc. unit on charges of falsifying test results on chemicals and drugs between 1969 and 1976.

An eight-count indictment alleged that four defendants altered test results of studies conducted on mice and rats. The studies were for three companies seeking federal approval for the chemicals and drugs.

Charged in the indictment were: Joseph C. Calandra, former president of the Bio-Test concern; Moreno L. Keplinger, former manager of toxicology; Paul L. Wright, former section head of rat toxicology, and James B. Plank, former assistant manager of toxicology.

Lawyers for Messrs. Calandra and Wright said their clients would plead innocent to the charges and would defend themselves in court. Messrs. Keplinger and Plank were unavailable for comment.

Each of the four men was charged with three counts of mail fraud, one count of wire fraud and four counts of submitting false documents to the government. The mail and wire fraud charges carry maximum penalties of five years' imprisonment and a $1,000 fine; the false documents charges carry a maximum penalty of five years in jail and $10,000 in fines.

The indictment charged that the four men conducted studies on Sencor, a herbicide, and Nemacur, a pesticide, for Chemagro Corp., a division of Mobay Chemical Corp., and falsely reported the studies ran 18 months, when they really ran only 14 months. The indictment also said they underreported the number of animals tested.

A spokesman for Mobay, a Pittsburgh-based unit of Bayer AG of West Germany, said the concern has authorization from the U.S. Environmental Protection Agency to sell Sencor and Nemacur, and is doing so.

The former Nalco unit officials also were charged with falsifying results of tests on Trichlorocarbanilide, (TCC) an antibacterial agent used in deodorant soaps, and on Naproxen, an anti-inflammatory arthritis drug. Government prosecutors said the scientists concealed evidence that TCC produced atrophied testicles in mice that were fed the substance. The accused officials also are charged with falsifying data on blood and urine tests on Naproxen, according to the indictment.

The Food and Drug Administration said Naproxen and TCC have been tested and found safe, and both drugs are currently on the market.

A spokesman for Nalco said IBT Laboratories is "still in existence," working with the government and some companies on past studies. But he said the wholly owned subsidiary is "winding down" to prepare to cease operations.

Nalco has been named in four lawsuits in connection with the IBT Laboratories studies, according to the company's 1980 annual report. Mobay is suing Nalco for breach of contract and misrepresentation. The company denies liability for its unit's conduct, the report says. It also says Nalco made provision in its 1978 financial statements for discontinuing IBT Laboratories operations.

IBT
CMA

Brief Report

Hepatic Angiosarcoma

Possible Relationship to Long-term Oral Contraceptive Ingestion

Paul S. Monroe, MD; Robert H. Riddell, MD; Mark Siegler, MD; Alfred L. Baker, MD

• **A 32-year-old woman with an eight-year history of oral contraceptive use was found at laparotomy to have a hepatic angiosarcoma. The prolonged exposure to contraceptive hormones may have been a factor in the development of this rare tumor. The estrogens and progestins contained in oral contraceptives are biochemically similar to the anabolic-androgenic steroids that have recently been reported to cause hepatic angiosarcoma.**

(*JAMA* 1981;246:64-65)

THE USE of oral contraceptives has been associated with the development of a variety of hepatic tumors, including hepatic adenoma, focal nodular hyperplasia, and hepatocellular carcinoma.[1] We describe a patient in whom hepatic angiosarcoma developed after taking oral contraceptives for eight years. The increased incidence of hepatic angiosarcoma among users of androgenic-anabolic steroids[2] and the resemblance of vascular and hepatic parenchymal abnormalities in users of oral contraceptives to the precursor lesions of hepatic angiosarcoma suggest that this may be more than a chance association.

Report of a Case

A 32-year-old woman was admitted in May 1979 with a history of several episodes of severe right-sided abdominal pain occurring during two years. On admission she appeared well. An abdominal examination demonstrated an exquisitely tender liver but no bruits or rubs. Laboratory tests disclosed the following values: hematocrit, 41%; WBCs, 7,300/cu mm; differential cell count, normal; total bilirubin, 0.6 mg/dL; alkaline phosphatase, 53 IU (normal, 10 to 85 IU); aspartate aminotransferase, 18 IU; alanine aminotransferase, 8 IU; albumin, 4.0 g/dL; and globulin, 3.2 g/dL. The prothrombin time was not prolonged. The carcinoembryonic antigen and α-fetoprotein values were within normal limits. An oral cholecystogram was normal, but a technetium Tc 99m sulfur colloid liver scan showed multiple filling defects in the right lobe and a large cold area in the region of the porta hepatis, with slightly increased activity in this area during the arterial phase of the flow study. Hepatic ultrasound showed inhomogeneity of the posterior right lobe but no definite mass. Celiac angiography disclosed a large avascular lesion of the right lobe of the liver with a small central area that filled during the venous phase, suggesting a hemangioma or adenoma. The patient was gravida 2, para 2, and had used an oral contraceptive for eight years. She had not used oral contraceptives after a tubal ligation three years before admission. There was no history of exposure to vinyl chloride, anabolic steroids, thorotrast, or organic arsenic.

At laparotomy, many firm, white nodules involved both lobes of the liver. Biopsy specimens were taken, and a diagnosis of hemangioendothelial sarcoma (hepatic angiosarcoma) was made (Fig 1 and 2). While some areas of liver contained normal endothelial cells, other sections showed atypical Kupffer cells that were enlarged, hyperchromatic, and pleomorphic (Fig 3).

In the year after surgery, the pain had not recurred and the patient has felt completely well. A liver scan showed no progression of the disease. Because of the atypical course for an hepatic angiosarcoma, the histology slides and electron micrographs were reviewed by specialists at other institutions. All concurred in the diagnosis of angiosarcoma. In addition, immunoperoxidase staining of the tissue using a factor VIII antiserum was performed. This was strongly positive, confirming the endothelial origin of the tumor.

Comment

More than 300 cases of liver adenomas and focal nodular hyperplasia have been reported in women taking oral contraceptives.[1] Regression of

Fig 1.—Tumor nodule showing spectrum of endothelial cell changes ranging from spindle-shaped to ovoid, containing central nucleoli with incomplete vasoformation (hematoxylin-eosin, original magnification ×300).

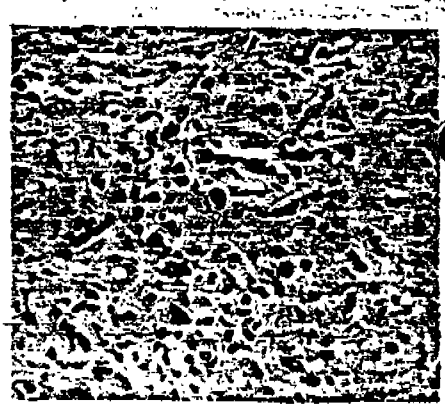

Fig 2.—More cellular part of second nodule in which tumor cells form capillary channels (arrow) containing RBCs. Electron microscopy confirmed that these were endothelial cells (hematoxylin-eosin, original magnification ×300).

Fig 3.—Biopsy specimen from grossly normal liver, demonstrating sinusoids lined with dyplastic Kupffer cells (arrow) (hematoxylin-eosin, original magnification ×500).

From the Liver Study Unit (Drs Monroe and Baker) and the Section of General Internal Medicine (Dr Siegler), Department of Medicine and the Department of Pathology (Dr Riddell), University of Chicago Hospitals and Clinics.

Reprint requests to Department of Medicine, University of Chicago, Box 400, 950 E 59th St, Chicago, IL 60637 (Dr Baker).

liver adenomas after cessation of hormonal therapy and recurrence of these tumors after surgical resection in patients who continue to use oral contraceptives suggest that these drugs are linked to the pathogenesis of this tumor.[1] The precise role of oral contraceptives in production of focal nodular hyperplasia is uncertain.[4] Oral contraceptives may also be a factor in causing malignant tumors of the liver, particularly since foci of hepatocellular carcinoma have been found within several liver adenomas.[1]

Hepatic angiosarcoma developed in the patient after using oral contraceptives for a total of eight years. In the year after diagnosis, she has had no progression of disease, in contrast to the short survival for most patients with hepatic angiosarcoma. The slow progression resembles the apparently indolent course reported for hepatocellular carcinoma associated with oral contraceptive use,[5] suggesting that the drug may have been a factor in causing and promoting growth of the tumor.

Additional factors support a possible etiologic relationship between oral contraceptives and hepatic angiosarcoma. First, hepatic angiosarcoma developed in a patient after using diethylstilbesterol for 13 years for the treatment of prostatic carcinoma.[6] Second, users of oral contraceptive pills have hepatic parenchymal and vascular changes that resemble precursor lesions of hepatic angiosarcoma, including hyperplasia of hepatocytes and sinusoidal cells, sinusoidal dilation, and peliosis hepatis.[1,2,7] These changes are similar to those produced in humans by vinyl chloride, arsenic, and thorotrast,[2,8] previously shown to cause hepatic angiosarcoma. Also, liver adenomas from women who use oral contraceptives demonstrate more extensive peliosis hepatis and arterial, intimal, and medial hypertrophy with occlusive phlebitis and thrombi than do tumors from nonusers of these medications.[1]

Third, users of androgenic-anabolic steroids, C-17-α-alkyl-substituted steroids that are closely related biochemically to the synthetic estrogens and progestins used in oral contraceptives, have been associated with the production of vascular and parenchymal changes resembling those seen in patients with oral contraceptive pill exposure, as well as probable precursor lesions of hepatic angiosarcoma and liver adenomas and hepatocellular carcinoma. In 168 cases of hepatic angiosarcomas, four patients were found to have had long-term androgenic-anabolic steroid exposure.[2] Further systematic study of patients with and without oral contraceptive pill exposure will be necessary to establish these drugs as an unequivocal cause of this rare tumor.

Hans Popper, MD, PhD, Peter Scheuer, MD, and Juan Rosai, MD, reviewed the histology slides and electron micrographs. Dr Rosai also performed immunoperoxidase staining of the tumor tissue.

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Computed Tomography for the Evaluation of Thoracic Masses in Children

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• **Large chest masses in two young children were evaluated using thoracic computed tomography (CT). Air was identified within the mass four days before it was visible on the plain roentgenograms in one patient. Rapid injection of contrast material with CT scanning demonstrated that the pulmonary blood flow passed through the mass, instead of being displaced by it, in the other child. Thus, both lesions were identified as originating in the pulmonary parenchyma rather than in the mediastinum.**

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PULMONARY consolidation may appear radiologically as a solid mass. Without invasive procedures, it may be difficult to determine whether such a lesion originates in the mediastinum or in the pulmonary parenchyma. Distal infection may accompany bronchial obstruction, so the presence of fever, cough, or leukocytosis does not exclude a neoplasm or congenital anomaly as a component of a chest mass. This is especially true in children, in whom pulmonary or mediastinal masses may reach mas-

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Phosgene in the Thermal Decomposition Products of Poly(Vinyl Chloride): Generation, Detection and Measurement

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Abstract

An analytical study was made to determine whether carbonyl chloride (phosgene) is formed during the thermal decomposition of poly(vinyl chloride), PVC. Four methods of decomposition were studied: (1) thermal degradation of PVC in a resistively heated furnace, (2) electrical overloading of a PVC clad wire, (3) electrical arcing between electrodes partially covered with PVC, and (4) electric arc initiated flaming combustion in a cup furnace. Results are reported which show that significant quantities of phosgene can be generated from PVC by the electric arc method. Lesser amounts were found in the other scenarios. The measurements, identification and quantification of phosgene in the decomposition product, were obtained through the use of gas chromatography, infrared spectroscopy and mass spectroscopy. While the study was not mechanistic in nature, phosgene is postulated to result from secondary reactions of the PVC products. Reaction mechanisms are suggested.

Introduction

Vinyl chloride polymers are frequently used in many applications, perhaps the most familiar application is for electrical insulation. These polymers are also widely used in construction, in appliances, in furnishings and in transportation vehicles. Total production for 1978 is estimated to be 2.3 million metric tons (1). Buildings, including home furnishings and appliances, provide the major market for the production.

The role of poly(vinyl chloride), PVC, in leading to human fire fatalities has been the subject of a number of investigations (2,3,4). In addition, the thermal degradation of PVC has been studied extensively from an analytical point of view (5,6) and various reviews of such studies have been prepared (7,8,9). Toxicological studies involving the exposure of animals to the thermal degradation products of PVC have also been reported (2,3).

Unanswered by these various studies is whether or not carbonyl chloride* is a product of thermal degradation of PVC. A toxicological study by Barrow et al (2) suggests that the toxicity of PVC decomposition products is due principally to HCl, with little contribution from other components. The work reported by Woolley (6) and Tsuchiya et al (5) seems to lend support to Barrow's conclusion. However, Woolley's negative results regarding phosgene are limited by an instrumental detectability of 50 ppm, a level that would be quite significant toxicologically (10).

On the other hand, Baltatis et al (11) reported the presence of phosgene in the combustion products of two PVC composite materials which were burned in a closed container. These workers reported that burning 0.5 g of PVC from conveyor belts and cables gave respectively 0.0019 and 0.0135 per cent of $COCl_2$ in a 5 liter chamber. Earlier Coleman and Thomas (12) reported $COCl_2$ concentrations up to 3 ppm and to 1 ppm respectively for unstabilized PVC and stabilized PVC composites burned at 900°C in a closed environment.

In fatal fires involving PVC, various claims have been made which attribute at least part of the toxicological hazard to phosgene (13,14). The bases for the claims, however, are not well documented in those reports. Nevertheless, the reports do raise a fundamental question that the analytical measurements referred to above do not clearly resolve, either as a consequence of instrumental limitation or the limitation imposed by the type of decomposition scenario chosen.

Based on these uncertainties and the toxicological significance of phosgene, a study was carried out in which analyses for $COCl_2$ were performed on decomposition products obtained by four methods, each of which represents a potential real situation.

The four methods are: (1) direct thermal degradation of PVC in a resistive furnace; (2) electrical overload of a copper wire wrapped with PVC insulation; (3) an electrical discharge between wires covered by PVC insulation; and (4) electric arc initiated flaming combustion in a cup furnace.

The first method is equivalent to the analytical type of studies already referenced in the literature. The most significant difference between this study and other work is that more sensitive analytical techniques were used in this study. More importantly, the second and third methods were not previously represented and were chosen based on expected modes of degradation involving electrical overload and arcing conditions (e.g. reference (7)).

* Carbonyl chloride whose formula is $COCl_2$ has three well known synonyms: phosgene, chloroformyl chloride and carbonic acid dichloride. In the following text the synonym phosgene and the formula are used interchangeably to denote this compound.

Experimental

Reference Gas

Reference gas mixtures containing about 60, 80, 110 and 600 ppm of $COCl_2$ were prepared in metal cylinders from the vapor of liquid $COCl_2$ and pressurized with nitrogen to 500 psi. The exact concentration of the individual reference gases is not known. However, the method of preparation, purity of the reagent gases and the expected stability lead to an estimated accuracy of about ± 5% (15).

PVC Composite Samples

The PVC composite materials used in this study were formulations commonly employed as electrical wire insulation. Typical formulations included about 45% PVC resin, 32% plasticizer, with the remaining fraction composed of fillers, pigments and stabilizers. The PVC resin used in this study was a commercial material whose reported values of number-averaged and weight-averaged molecular weights are 22,400 and 57,700, respectively.

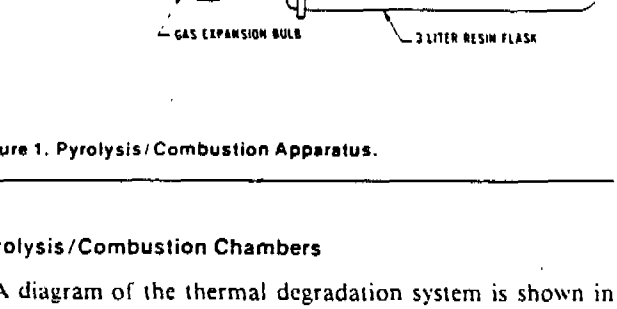

Figure 1. Pyrolysis/Combustion Apparatus.

Pyrolysis/Combustion Chambers

A diagram of the thermal degradation system is shown in Figure 1. The system consists of a 3 liter resin reaction flask, which could be opened and closed by a ground glass top which was fitted with standard tapered joints. For the first group of experiments, the PVC was thermally degraded in a resistively heated furnace. A quartz boat, used as the sample holder, was positioned within the furnace and located near the center of the chamber. A rubber septum was fitted to one of the standard tapered joints through which gas samples were taken from the chamber by a gas-tight hypodermic syringe. To accommodate the pressure increase in the chamber during thermal decomposition, a rubber balloon was attached to another joint in the flask cover as shown.

For the electrical overload heating of PVC samples, the furnace resistive elements were replaced with a PVC insulated copper wire. A power supply was used to heat the wire by a current overload. Dual strands of number 12 copper wire, about 10 cm in length, connected the power supply to a 10 cm coil of number 12 copper wire. The coil was coated with PVC insulation.

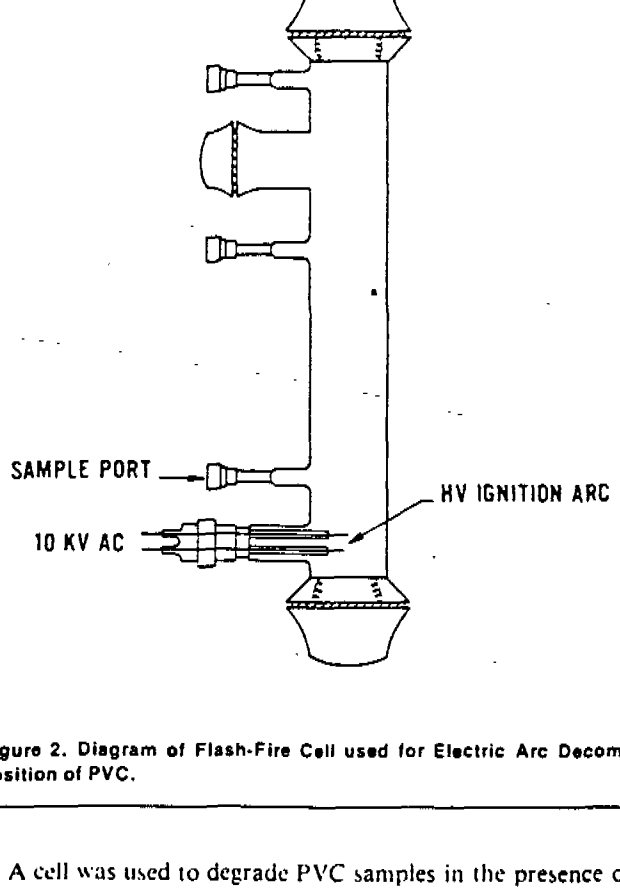

Figure 2. Diagram of Flash-Fire Cell used for Electric Arc Decomposition of PVC.

A cell was used to degrade PVC samples in the presence of an electric arc. The cell, shown in Figure 2, was designed to study the flash-fire potential of materials. This system was constructed of a Pyrex cylinder 50 cm in length and 5 cm in diameter having a volume of about one liter. The ends of the cylinder were fitted with spring-loaded covers sealed by O-rings. Parallel platinum electrodes about one centimeter in length were located near one end of the cell to which a 10 kv AC power supply was connected for the generation of an electric arc for the decomposition of PVC. The cell also contained sampling ports, each with a rubber septum, which were located near the ends and middle of the cell.

Analytical Instrumentation

In this study, the analytical instrumentation consisted of gas chromatography (GC), infrared spectroscopy (IR), and a gas chromatography-mass spectroscopy-minicomputer (GC-MS-MC) system.

The primary GC measurements of phosgene were accomplished with an instrument equipped with a linearized electron capture detector (ECD). The GC was fitted with a glass column about 2 meters in length and 2 mm i.d. which was packed with an acid treated silica gel (Chromosil 310). Esposito et al (16) had previously shown that this packing provides good recoveries and resolution in GC determinations of $COCl_2$ in air. The column was maintained at 70°C. The carrier gas was 5% methane in argon at 30 ml/minute. A second column packed with 30% diisodecyl phthalate on a solid support (Chromosorb W) was used at about 50°C for confirmation of the measurements using the Chromosil 310 packed column. The chromatograph was interfaced with a

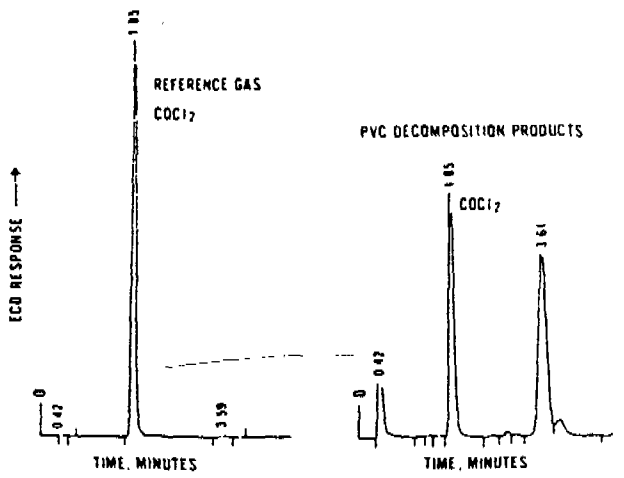

Figure 3. Chromatograms Obtained from Silica Gel Packed Column showing $COCl_2$ Peak in Reference Gas and PVC Decomposition Product.

recording integrator (printer/plotter).

In the GC/MS/MC system, the quadrupole spectrometer was equipped with an electron impact ionization source which, along with the MS electrometer, served as the system's GC detector. This GC was interfaced to the MS by a membrane separator and was fitted with the silica gel packed column maintained at 70°C. Helium was used as the carrier gas at a flow rate of 30 mL/min. The infrared spectrophotometer employed in obtaining spectra of PVC decomposition products and phosgene was a high resolution grating instrument having a wide range of capabilities for scan speed and scale expansion. Typically, the scan speed and slit program or resolution were set at values deemed appropriate for quantitative determinations. The spectra were recorded with the ordinate scale expansion set at 10x in the linear absorbance mode.

Methods of PVC Decomposition and Sampling for $COCl_2$

Approximately 0.6 g of PVC were placed in the quartz boat and ignited with the resistance heater. To achieve ignition, the furnace was heated to a bright red color or until ignition of the PVC occurred, which was approximately 1 to 2 minutes after applying the voltage to the heater. After ignition, the power to the heater was terminated and the sample was allowed to burn until it self-extinguished or the sample was consumed. The degree of combustion depended on the formulation but was consistent within a given formulation.

After extinguishment, 0.1 to 0.2 mL of the gaseous products were drawn from the chamber with a gas tight syringe and injected into the gas chromatograph for analysis. From the resulting chromatogram, the $COCl_2$ peak areas and retention times were calculated by the integrator interfaced with the chromatograph. The concentration of the $COCl_2$ in the decomposition products was then computed from calibration data obtained from the ECD response to known quantities of $COCl_2$ reference gases.

In some cases infrared spectra were made of the decomposition products following extinguishment of the PVC sample. For the IR measurements the decomposition products were expanded or introduced into an evacuated one-meter folded-path length gas cell which was equipped with KBr windows and gold front surface mirrors.

The decomposition of the PVC by an electrical overload was accomplished by applying power to the PVC clad coil in the sample chamber for a period of about 3 to 5 minutes, or until decomposition was complete. Sampling of the products and analysis of these products were accomplished by the technique described for the resistively heated furnace experiments.

For the electric arc study, a piece of PVC insulation approximately ½ cm long was placed on an electrode in the "flash-fire" cell. A 10 kv ac potential was applied between the electrodes until the sample was degraded. The gaseous degradation products were analyzed as described previously.

The GC method of analysis for $COCl_2$ in PVC degradation products was also applied to gases taken from a 200 l animal-exposure chamber in which a PVC composite (electrical insulation) was degraded by flaming combustion. The details of the animal exposure study are the subject of another study to be reported at a later date.

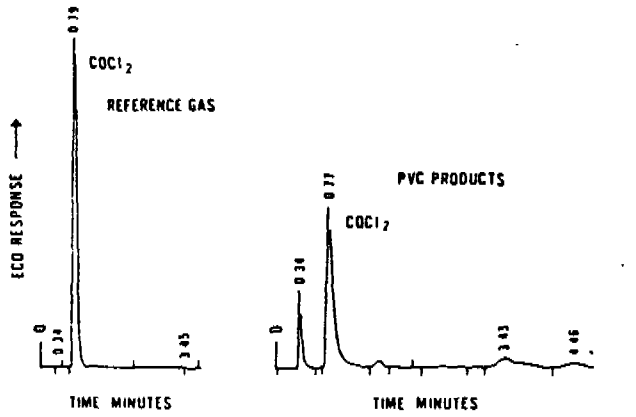

Figure 4. Chromatograms Obtained from Phthalate Ester/Solid Support Column showing $COCl_2$ Peak in Reference Gas and PVC Decomposition Product.

Results and Discussions

Identification of Phosgene

Identification of phosgene in PVC decomposition products was accomplished primarily by employing gas chromatography. Additionally confirmation evidence of this product was obtained through infrared spectroscopy and mass spectroscopy.

Figure 3 represents a typical chromatogram of the phosgene reference gas, and a chromatogram of a product gas mixture generated from PVC in air by the electric arc method. It is apparent that the retention time of a peak near 1.8 minutes in the PVC decomposition products corresponds to the retention time of $COCl_2$ in the reference gas chromatogram. To confirm that the peak at 1.8 minutes is $COCl_2$, a second column material with different properties was used. Component characterization by retention times in two columns of different polarities is generally considered positive identi-

cation of an unknown compound (e.g. reference 17). For this confirmation, the GC was equipped with the diisodecyl phthalate/Chromosorb W packed column. Figure 4 shows chromatograms obtained using the column packed with the phthalate ester/solid support for the reference $COCl_2$ gas and the products of another PVC decomposition. As noted in the figure, the peak with the retention time of 0.77 minutes in the decomposition products is essentially the same as the retention time of $COCl_2$ in the reference gas.

For the mass spectral identification of phosgene in the PVC products, mass spectra were obtained of components eluting from the GC equipped with the silica gel packed column at the retention time of $COCl_2$. Figure 5 shows a total ion current chromatogram which represents the total ions generated by the mass spectrometer in the range m/e 33 to 150 as the $COCl_2$ reference eluted from the chromatograph. The peak at 2 minutes is $COCl_2$ and the peak at 0.4 minutes was found to be 1,1 dichloroethane, an impurity, whose parent ion m/e 98 and base peak m/e 63 are the same as $COCl_2$. In Figure 6 chromatograms of the total ion current and a single ion, m/e 63, are shown for PVC decomposition products generated by an electric arc. The peaks at 2 minutes correspond to the retention time of the $COCl_2$ reference. It was also feasible to monitor all of the major m/e ions of $COCl_2$ by the use of the computer interfaced with the GC/MS. The major ion

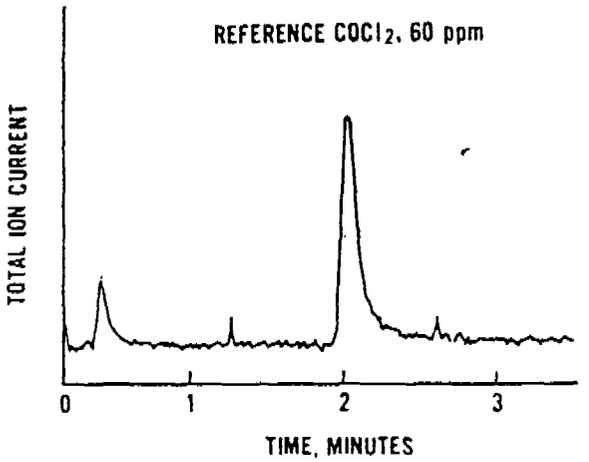

Figure 5. Mass Spectral Total Ion Current for $COCl_2$ Reference Eluting from GC Column.

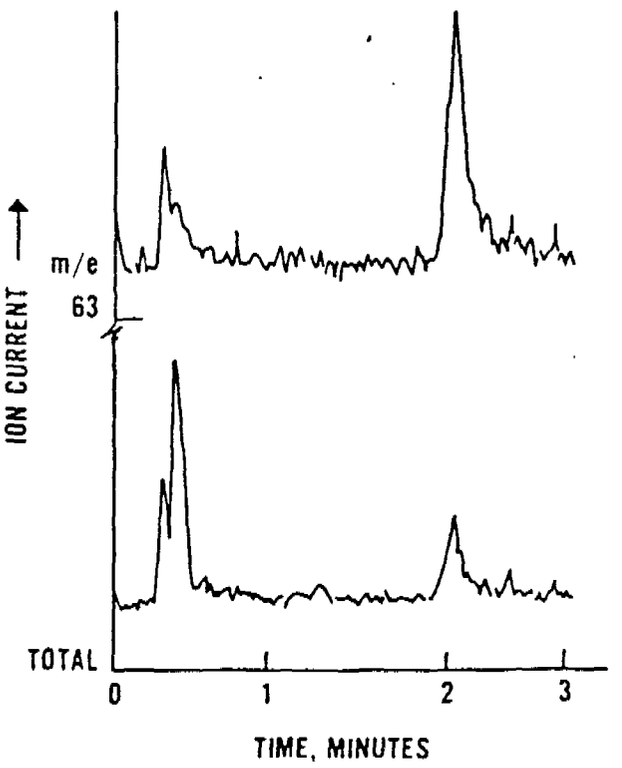

Figure 6. Mass Spectral Total Ion Current and Fragment m/e 63 Ion Current of Component of PVC Product Eluting from GC at Retention Time of $COCl_2$.

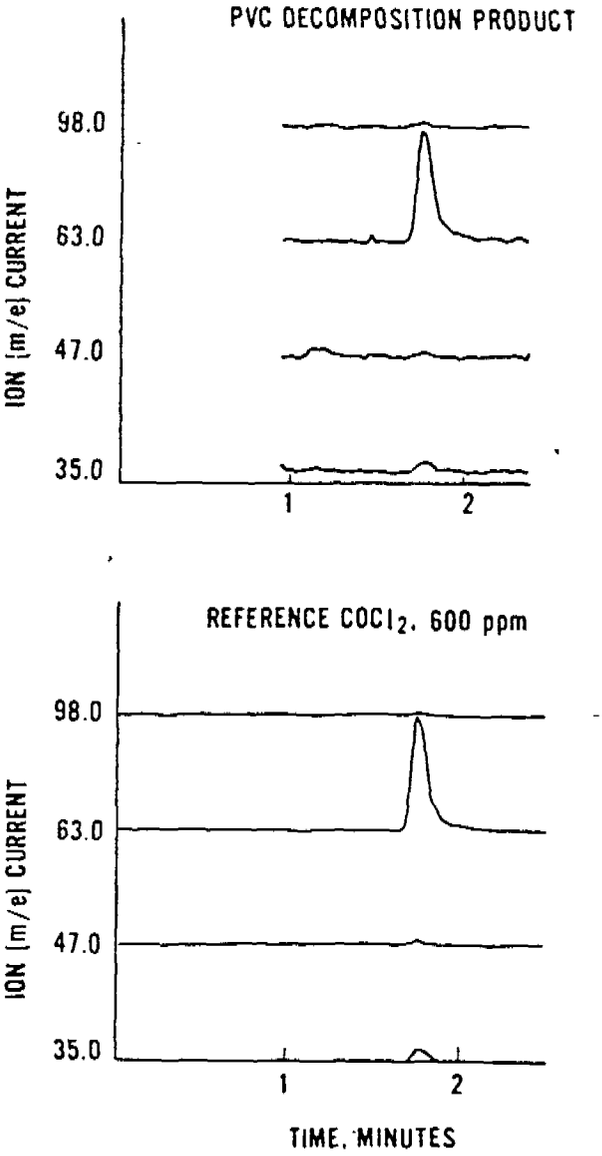

Figure 7. Major Ions of $COCl_2$ Monitored in Chromatograms of $COCl_2$ and a PVC Decomposition Product.

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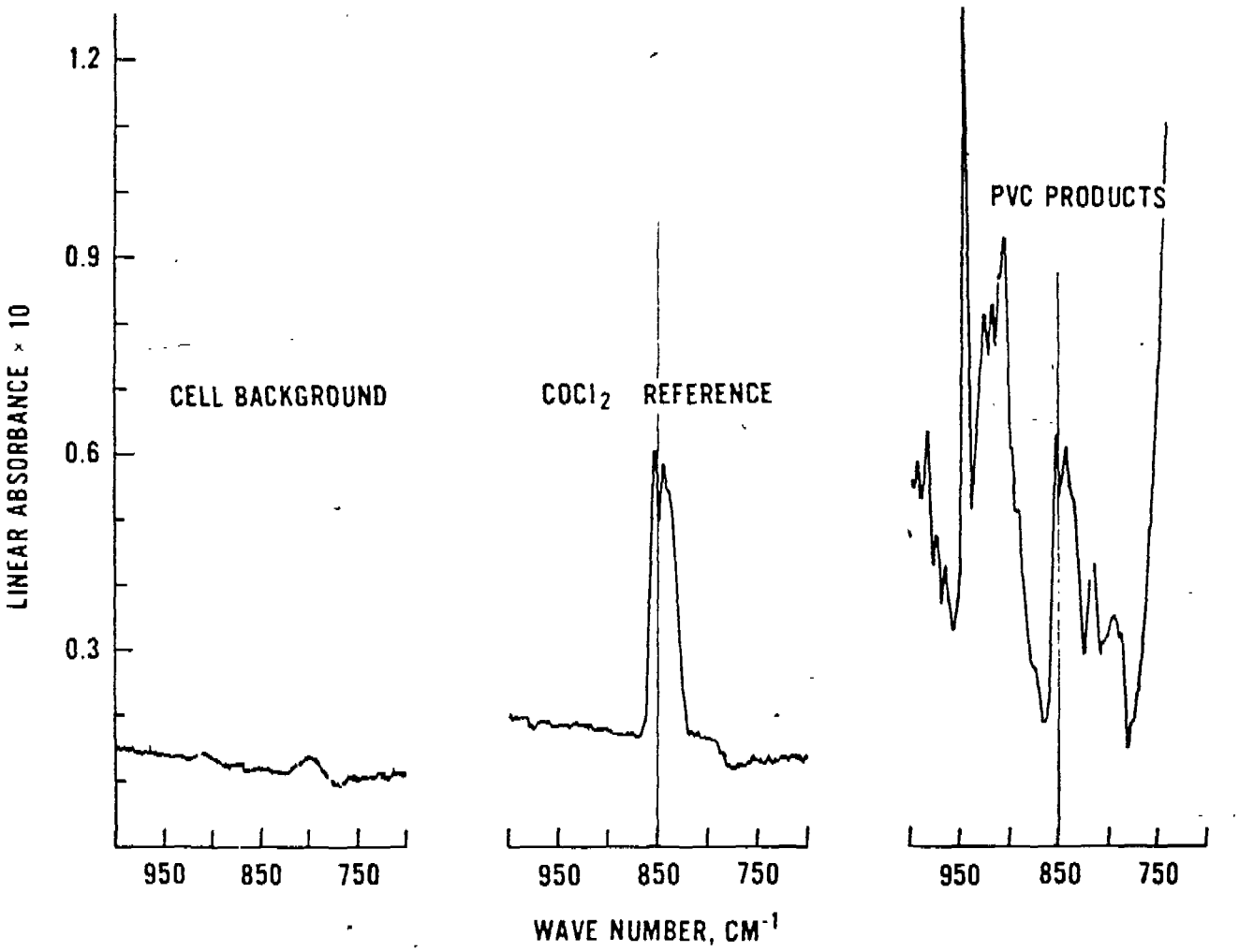

Figure 8. Infrared Absorbance Band of $COCl_2$ near 845 cm^{-1}.

fragments of $COCl_2$ are m/e 35 (Cl^+), 47 (CCl^+), 63 ($COCl^+$), and 98 ($COCl_2^+$). This result is demonstrated in Figure 7 for $COCl_2$ reference gas and the component in the PVC products which has the retention time of $COCl_2$. Here the $COCl_2$ retention time (about 1.7 minutes) is slightly less than the previous case (about 2 minutes) as a result of a small increase in the helium flow rate. This body of evidence corroborates the chromatographic identification of phosgene as a component in the decomposition products of PVC.

The infrared evidence of $COCl_2$ as a decomposition product of PVC is shown in Figure 8 by an absorbance band of $COCl_2$ and the same band in the decomposition products spectra. This band arises from the Cl-C-Cl stretching vibration (ν_4) of phosgene and is centered near 845 cm^{-1}. Generally the samples were scanned from about 950 cm^{-1} to 750 cm^{-1} which was sufficient to obtain the absorbance due to phosgene in this region.

The presence of phosgene in the decomposition products of PVC has been shown from different perspectives by three independent analytical techniques. The GC results alone provide convincing evidence for the presence of phosgene. However, the mass spectral and infrared data unequivocally corroborate this conclusion.

Quantitative Measurements of $COCl_2$

Figure 9 is given in order to show the response of the ECD equipped gas chromatograph to various quantities of $COCl_2$ reference gas. Here the resulting peak areas are plotted against the calculated volume of $COCl_2$ in N_2 which was injected into the chromatograph from a 100 μL syringe. These data were fitted to a line by linear least squares. The result of this fit gave the ECD response as 1.53×10^{-6} nanoliters (nL) per area unit. The correlation coefficient of 1.05 was obtained from the fit of these data. The response curve demonstrates that the ECD response is essentially linear at least to 12 nL of $COCl_2$. Although the response of the ECD to $COCl_2$ may be viewed as a calibration, in practice the sensitivity of the ECD was determined for each decomposition experiment.

The results shown in Table I are the results obtained from the combustion/pyrolysis of various PVC samples in the 3 l chamber furnace arrangement. The concentrations of $COCl_2$ shown in column 2 are derived from GC analyses of 0.1 to 0.2 ml gas samples of the decomposition products taken from the chamber at various times after the initial sample heating. In column 3, the weight ratios (mg/g) of $COCl_2$ to PVC were calculated as a means of normalizing the various quantities and PVC formulations to the estimated total amount of $COCl_2$ formed in the decomposition process. The weight

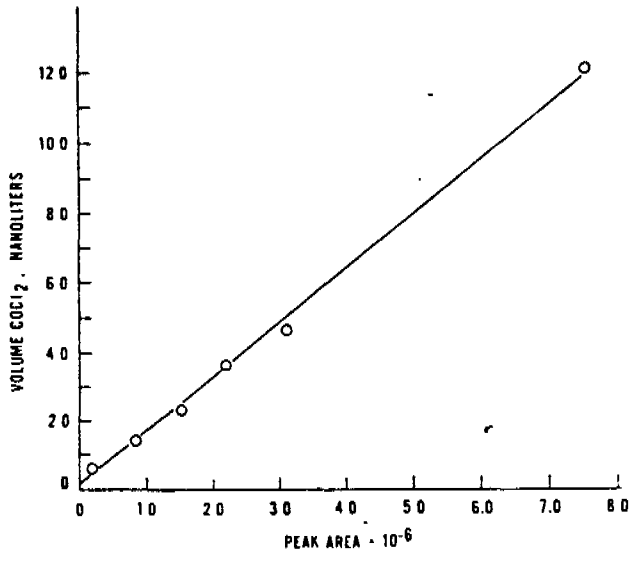

Figure 9. Response of ECD to $COCl_2$.

ratios of $COCl_2$ to PVC loading is seen to be of the same order of magnitude for the two composite samples. When the actual amount (about 45%) of PVC resin in the composite is considered, the $COCl_2$/PVC ratio is near that calculated for the homopolymer, PVC resin.

Table II gives the replicate results obtained from GC analyses of PVC combustion products from a 200 l animal-exposure chamber. Column 3 refers to the times that evacuated sampling bulbs were equilibrated to the pressure in the animal-exposure chamber. The ratios of $COCl_2$/PVC are similar to those reported in Table I. Here the PVC combustion was accomplished using a "Potts furnace" (18) heated to 500°C and equipped with an electric arc ignition source to insure flaming combustion. Details of this experiment are the subject of another study which is to be reported.

Table I. Chromatographic Estimation of $COCl_2$ Levels in Products of PVC Thermally Decomposed in a 3 Liter Chamber.

Sample/ Weight	[$COCl_2$], ppm (v/v)	$COCl_2$/PVC, mg/g	Remarks
Composite A:			
Run I (0.78g)	6	0.09	Sampled at 3 min.
	7	0.10	Sampled at 21 min.
Run II (0.67g)	5	0.09	Sampled at 3 min.
Run III (0.59g)	~ 0.5	~ 0 01	Sampled at 4 min.
	3	0.06	Sampled at 17 min.
Composite B.			
Run I (0.63g)	6	0.12	Sampled at 4 min
	2	0.04	Sampled at 12 min.
	~ 0.6	~ 0.01	Sampled at 26 min.
Run II (0.72g)	6	0.10	Sampled at 3 min.
	7	0.12	Sampled at 7 min.
	2	0.03	Reheated 3 min., sampled at 30 min.
Run III (0.63g)	6	0.12	Sampled at 4 min.
	2	0.04	Sampled at 12 min.
PVC Resin:			
Run I (0.26g)	~ 0.3	~ 0.01	Sampled at 4 min.
	2	0.09	Reheated 6 min., sampled at 30 min.
	3	0.14	Sampled at 10 min.
Run II (0.38g)	~ 0.2	< 0.01	Sampled at 5 min.
	2	0.06	Sampled at 10 min.

Table II. Chromatographic Estimation of $COCl_2$ Levels of 200 Liter Animal-Exposure Chamber After Flaming Combustion of PVC Composite C.

Experiment No.	($COCl_2$) ppm	$COCl_2$/PVC mg/g	Remarks
I. 4.0g Sample	0.55	0.11	Bulb filled at 3 min.
	0.50	0.10	Bulb filled at 7 min.
	0.55	0.11	Bulb filled at 13 min
II. 7.0g Sample	1.28	0.15	Bulb filled at 19 min
	1.26	0.14	Bulb filled at 23 min.
	1.26	0.14	Bulb filled at 30 min.

The results shown in Table III were obtained on products evolved from PVC wire insulation which was pyrolyzed solely by the heat produced by the electrical overload on the wire. It is seen that the ratios of $COCl_2$/PVC are about the same magnitude as those in the combustion/pyrolysis degradation in this chamber (Table I).

A marked increase in the levels of $COCl_2$ was found in the products when PVC was degraded by an electric arc. The results of these experiments are listed in Table IV. Run I of sample B showed the highest levels of phosgene. The reason for the higher concentration in this particular run is not known at this time.

Table III. Gas Chromatographic Estimation of $COCl_2$ Levels in Pyrolyzate of PVC on Electrically Over Loaded Wires in a 3 Liter Chamber.

Sample	[$COCl_2$], ppm, (v/v)	$COCl_2$ PVC, mg/g	Remarks
Composite D.			
Run I (0.45g)	< 0.1	—	Heated 3 min., sampled at 4 min.
	1.3	0 04	Sampled at 60 min.
	3	0.08	Reheated 3 min., sampled at 66 min
Run II (0.45g)	< 0.1	—	Sampled at 2 min.
	4	0.11	Reheated 3 min., sampled at 15 min.
	6	0.16	Sampled at 4 min.
Composite E:			
Run I (0 53g)	< 0.1	—	Heated 3 min., sampled at 4 min.
	4	0.09	Reheated 2 min., sampled at 21 min
	2	0.05	Sampled at 30 min.

Table IV. Chromatographic Estimation of Level of $COCl_2$ in Products of PVC Decomposed by an Electric Arc in 1 Liter Chamber.

Sample/ Weight	($COCl_2$), ppm(v/v)	$COCl_2$/PVC, mg/g	Remarks
Composite E:			
Run I (0.11g)	4	0.15	Sampled at 4 min.
	39	1.5	Sampled at 24 min.
	29	1.1	Sampled at 84 min.
Run II (0.24g)	4	0.07	Sampled at 4 min.
	32	0.56	Sampled at 6 min.
	23	0.40	Arc on 3 min., Sampled at 24 min.
Composite A:			
Run I (0.21g)	15	0.3	Sampled at 3 min.
	11	0.22	Sampled at 25 min.
Run II (0.21g)	17	0.34	Sampled at 70 min. (IR Cell)
Run III (0.21g)	35	0.70	Sampled at 15 min.
Composite B:			
Run 1 (0.18g)	70	1.6	Sampled at 5 min
	56	1.3	Sampled at 15 min.
Run II (0.19g)	14	0.28	Sampled at 12 min.
Run III (0.21g)	11	0.22	Sampled at 20 min. (IR Cell)

Table V. Extinction Coefficients $E_{855cm^{-1}}$ of $COCl_2$ IR Absorption from GC Determined Concentrations.

$[COCl_2]$, ppm	Absorbance x 10^2 at 855cm^{-1}	E, (ppm-m^{-1}) x 10^3
10	1.5	1.72
18	2.9	1.61
	3.0	1.58
33	4.4	1.33
29	4.2	1.48
32	4.2	1.39
35	5.7	1.64
		Avg. = 1.53
		Std. Dev. = 0.14

The R branch absorbance (maximum at about 855 cm^{-1}) of the $COCl_2$ ν_4 band was used for the quantitative measurements of this compound in the PVC decomposition products. The extinction coefficient for the absorbance at 855 cm^{-1} was derived from the absorbance of known volumes (50 mL aliquots) of 110 ppm $COCl_2$ in N_2 which were injected into the one-meter folded-path length sample cell. Table V summarizes these results. The trend toward lower coefficients at higher $COCl_2$ concentrations suggests that $COCl_2$ was undergoing decomposition in the IR cell.

Table VI compares the estimations of $COCl_2$ levels found in additional combustion/pyrolysis and electric arc experiments by infrared and chromatographic techniques. Generally, there is good agreement between the concentrations determined by GC and IR methods, although in some cases, the IR method gave lower values of phosgene. It should be noted, however, that the primary purpose of the IR analysis was qualitative

Table VI. $COCl_2$ in PVC Pyrolyzates Estimated by IR and GC Techniques.

Decomposition Method	Sample/ Weight	$[COCl_2]$, ppm (v/v) IR analysis	GC analysis
Electric Arc	Composite A:		
	Run I (0.17g)	27	25
	Run II (0.14g)	10	11
	Composite B:		
	Run I (0.20g)	54	91
	Run II (0.18g)	21	39
	Run III (0.17g)	13	19
Furnace	Composite A:		
	Run I (0.61g)	1	3
	Composite B:		
	Run I (0.59g)	5	7
	Run II (0.63g)	1	3

confirmation of the GC findings. A significant part of this difference may be attributed to the time required to obtain the respective chromatograms and spectrograms; the GC samples generally were taken from the IR cell before the scans of the 855 cm^{-1} band were made. The use of infrared spectroscopy for qualitative and quantitative determinations of $COCl_2$ in this study was not the method of choice with respect to ease of sample handling and analysis time required. However, spectroscopy did provide an independent means for confirming the presence of $COCl_2$ in PVC decomposition products and estimating its concentration.

The results of the above measurements show various quantities of $COCl_2$ are produced during the combustion/pyrolysis and electric arc decomposition of PVC in air when PVC is degraded under the experimental conditions described. The yield of $COCl_2$ from the combustion type experiments was low (0.06 to 0.15 mg/g). The concentration of $COCl_2$ was of the order of 0.5 to 1.3 ppm (Table II) when a sufficient mass of PVC was degraded (4 to 7 g decomposed in 200 l chamber) to produce significant adverse effects on animals. This concentration of $COCl_2$ is low and by itself is not considered to be the major cause of the observed toxicity. However, as noted in Table IV, the electric arc experiments produced 10 to 20 times more $COCl_2$ than the combustion/pyrolysis experiments. This concentration (30-50 ppm) has obvious toxicological implications.

The toxicological significance of the above analytical data can be estimated from the reported toxicity of phosgene in air (10). Concentrations of the order of 3 to 5 ppm cause effects to the eyes and throat, 25 ppm is dangerous for 30 to 60 minute exposure, and 50 ppm is rapidly fatal even after a short exposure. This information suggests that electric arc experiments can produce toxicologically significant concentrations of $COCl_2$. However it should be noted that exposure of animals to PVC decomposition products generated by an electric arc have not been carried out to establish the toxicological significance of this finding nor have experiments been performed to establish whether other products of significance may also be produced that are unique to an electric arc. Additionally, the results of the electric arc decomposition of PVC insulation have not been investigated by full scale studies.

Precursors for $COCl_2$ Formation

The reaction mechanisms for the formation of phosgene during the decomposition of PVC were not explored during this investigation. Stull (19) showed by thermodynamically calculated equilibrium for phosgene, chlorine, and carbon monoxide that the mole fraction of phosgene rapidly decreases as the temperature is raised significantly above 200°C. On the other hand, the environment around or near a PVC material undergoing pyrolysis and combustion is seen to consist of a complex mixture and is not expected to approach equilibrium conditions. Nevertheless, phosgene may be formed by secondary reactions involving the decomposition products of PVC at various proximities to the "decomposition plasma".

David and Staley (20) have summarized methods by which phosgene may be prepared. Included is the reaction of metal halides (MCl_2) with carbon monoxide.

$$(1)\ CuCl_2 + CO \rightleftharpoons Cu + COCl_2$$

At temperatures of 450°C to 750°C, copper chloride and carbon dioxide are also reported to yield phosgene in quantities as great as those with carbon monoxide.

Additionally, Gmelins Handbuch (21) shows that chlorine may be generated from HCl according to the following equation:

$$(2)\ 4HCl + O_2 \underset{}{\overset{320° - 400°C}{\rightleftharpoons}} 2H_2O + 2Cl_2.$$

Chlorine in the presence of carbon (soot) reacts with carbon monoxide to form phosgene (22).

$$(3)\ CO + Cl_2 \rightleftharpoons COCl_2$$

The above sequence of reactions, although unexplored in this investigation, suggests possible routes by which phosgene may be formed as a result of PVC decomposition, especially in electrical fires. It can be postulated that a high intensity electrical discharge could produce vapors of copper and copper chloride in presence of PVC as precursors to carbonyl chloride. Similarily, the question is raised whether antimony chloride, generated from antimony oxide added to PVC as a fire retardant, would also contribute to $COCl_2$ production.

It appears that the established processes for the formation of phosgene cannot occur directly by fragmentation or depolymerization of the polymer $(-CH_2CHCl-)_n$ and subsequent oxidation of the fragment to $COCl_2$, or by concerted reactions of oxidation and depolymerization. This indicates that phosgene is formed by a secondary reaction involving the pyrolyzates and oxygen. Since the greater amount of phosgene is found by the electric arc decomposition, the process of formation through a free radical mechanism or highly activated components, is suggested. The parameters influencing the quantities of phosgene formed may include current density, experimental scale and PVC formulation.

Conclusions

The use of gas chromatography, infrared and mass spectroscopy, and gas chromatography in concert with the latter two has confirmed that phosgene can be generated by thermal degradation of PVC, especially in electrical fires. The process by which this substance is generated remains an unanswered question. The levels of $COCl_2$ found in the products of PVC generated by an electric discharge show that this substance may be produced in significant quantities in electrical fires involving PVC. This study suggests that additional investigations need to be undertaken to determine the factors or parameters that influence the amount of phosgene produced during thermal decomposition of PVC and other chlorine-containing polymers.

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The few experimental studies that have been reported present conflicting data on PVC toxicity. This may be due to the different formulations of PVC examined and/or differences of experimental designs. In the only previously reported inhalation study,[1] the authors suggest that continuous (24 hr) exposure of guinea pigs for 2-7 months in a PVC bagging plant resulted in the formation of granulomatous foci in the lung. The nature of the PVC used in that study—possibly a mixture of homopolymer and paste polymer—is not described, and the level of exposure is poorly defined.

Using a simple in vitro technique of hemolysis it has been shown that different formulations of PVC exhibit differential biological potential, as assessed by their ability to react with red blood cell (RBC) membranes.[2,3] Thus, homopolymers are not hemolytic, whereas paste polymers containing surfactants (detergents) on their particle surface produce extensive RBC damage in vitro. The chemical formulation of the detergent used in the preparation of the PVC polymer was, therefore, considered important in its hemolytic reaction.[3] Similar findings were reported by other investigators[4,5] who found that certain emulsion (paste) polymers were cytotoxic to rat peritoneal macrophages maintained in vitro, which is a test system considered by some investigators to be indicative of particle fibrogenicity in vivo. These investigators,[5] however, subsequently concluded that some paste polymers containing detergents produce a "false-positive" result in the in vitro system because the intratracheal 2-mg injection of the identical polymers into rat lungs produces no progressive fibrogenic response (unlike α quartz). All the polymers tested in experimental animals produce only a mild inflammatory response, and it was therefore concluded that PVC per se is an inert material.[5]

Intratracheal instillations of high doses (25 mg) of PVC have been shown to induce biochemical and histopathological changes in rat lung tissue;[6] other studies[7] have indicated that the cellular and biochemical effects at the alveolar surface and in lung tissue of instilled PVC particles are dose-dependent. However, aggregates of PVC dust given intratracheally, like many other materials given in this way, can produce a different, usually more vigorous, response from that produced by inhaled dust. Additionally, it is not possible to convert a single intratracheal instillation of a known volume of dust to a period of exposure at a multiple or fraction of the dust level, which means that for assessing safe occupational exposure levels, the results from intratracheal instillation studies are open to critical interpretation.

The aim of the present study was to determine whether the inhalation of a paste polymer, PVC-7, containing the detergent sodium dodecyl sulphate,[3,7] at "nuisance" dust level (10 mg/m^3) would produce any alteration in the lungs of experimental animals. The parameters chosen for investigation included a study of the biochemical integrity of the alveolar surface by estimation of free cell number and enzyme activities, and determination of pulmonary surfactant levels and soluble protein. In addition to histopathological examination of the lung, DNA, and protein 'synthesis' and hydrolytic enzyme activity of alveolar tissue were monitored.

MATERIALS AND METHODS

Animals. Eighty 10-wk-old female albino rats of the Sprague Dawley C.D. strain (Charles River, U.K. Ltd., Margate, Kent) were used in this study. These were randomly allocated to either the control or PVC-exposed group so that each group consisted of 40 rats. The rats were housed in groups of four, in polypropylene cages with stainless steel mesh floors. Food and water were supplied ad libitum while the rats were in the cages. The room temperature was maintained at 20 ± 2°C, and lighting was controlled to provide a 12-hr light period each day.

Aerosol exposure. A paste polymer, PVC-7, which contains sodium lauryl (dodecyl) sulphate surfactant was used throughout the study. The PVC-treated animals were exposed to a mean aerosol concentration of 10 mg/m^3, i.e., "nuisance" dust level (Guidance Note EH 15/77, Health and Safety Executive), on 5 days for 6 hr/day for 5 days/wk up to 15 wk. Groups of 10 exposed rats were examined with control animals at 3, 9, and 15 wk after the experiment was initiated. One group of animals was maintained without further contact with PVC for 15 wk after being previously exposed to the dust for 15 wk. A nonexposed control group was also maintained during this time period.

Exposures were carried out in a perspex, cubic, 240-L chamber which was operated under dynamic conditions at a slight positive pressure. The aerosol of PVC particles was generated using a Wright dust feed mechanism (L. Adams Ltd.; Minerva Road, Chase Estate, London NW10). Following preliminary experiments to determine optimum operating conditions, a dust packing force of 0.2 tons was used. The mechanism was operated with standard canister liner at a gear ratio of 4 : 1 reduced. Total chamber air was supplied through the dust feed which was run at 1.05 kg/cm^2 (25 L/min). The aerosol was introduced into the exposure chamber at the base center and then ascended through an area clear of holding cages to descend through the cages in which the animals were individually housed, and left the chamber through a series of holes at the base. The chamber was held in a fume cupboard which was at negative pressure with respect to the laboratory, and the exhausted dust was removed by an absolute filtration unit. Control animals were placed in an identical chamber, but were exposed only to the same compressed air as that used to operate the dust feed mechanism. Aerosol concentration was determined twice daily by gravimetric analysis of samples collected with an openface filter holder operated in the vertical position. Due to the extremely low aerosol concentration, a sampling rate of 10 L/min was required to ensure accurate assessment of total chamber concentration. The particle size distribution in the chamber was measured using an Anderson mini-sampler.

Treatment of animals prior to biochemical analyses. In the biochemical studies six exposed and six control rats were examined at each chosen time interval and treated identically.

Each animal was given an intravenous tail vein injection of 75 μCi of [methyl-^{3}H]-thymidine (52 Ci/mmol) and 2.5 μCi of L-[U-^{14}C]-proline (282.5 mCi/mmol) and left

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Effects in the Rat of Inhaling PVC Dust at the Nuisance Dust Level (10 mg/m^3)

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ABSTRACT. Rats inhaled a paste polymer polyvinyl chloride dust at an aerosol concentration of 10 mg/m^3 for 6 hr/day, 5 days/wk for a 15-wk period. A small number of randomly scattered lung lesions were detected at 15 wk; these lesions were also present 15 wk after exposure to polyvinyl chloride had ceased. Few if any biochemical changes were detected at the alveolar surface in lung tissues or other organs of polyvinyl chloride-exposed rats. It is therefore concluded that at "nuisance" dust level this form of polyvinyl chloride polymer exhibits a weak biological reactivity.

DURING ONE STAGE in polyvinyl chloride (PVC) manufacture the material exists as a fine, easily respirable dust. Consequently, investigators have examined the effects of this dust on mammalian lung.

Table 1.—Cellular and Biochemical Studies on Rats Exposed to 10 mg/m^3 PVC Dust for Different Time Periods

Exposure Period/ Animal Group	Lung Weight/ Body Weight Ratio x 10^2	Number Free Cells/Animal x$.10^{-6}$	Pulmonary† Surfactant mg/Animal	Pulmonary† Lavage Protein mg/Animal	Acid RNAase units/10^6 Cells	Acid RNAase units/g Lung	DNA mg/g Lung
3 Weeks							
Control	0.53 (±.086)	6.71 (±0.93)	0.50	2.25	0.68 (±0.12)	74 (±10)	4.54 (±0.76)
PVC-Exposed	0.55 (±.082)	8.86 (±1.52)	0.52	2.62	0.69 (±0.29)	75 (±19)	4.06 (±0.43)
3 Weeks							
Control	0.47 (±.036)	19.35 (±4.64)	0.60	3.19	1.17 (±0.27)	108 (±12)	4.93 (±1.07)
PVC-Exposed	0.48 (±.037)	13.79 (±4.63)	1.50*	3.96	1.39 (±0.31)	104 (±12)	5.30 (±0.87)
15 Weeks							
Control	0.43 (±.023)	11.00 (±3.61)	0.66	2.86	0.90 (±0.31)	83 (± 5)	4.01 (±0.87)
PVC-Exposed	0.40 (±.045)	11.00 (±1.08)	0.62	3.11	1.10 (±0.21)	104 (±16)*	4.78 (±0.32)
15+ Wk							
15 Wk Clearance							
Control	0.39 (±.028)	9.26 (±2.93)	1.28	3.50	0.96 (±0.22)	45 (± 8)	4.23 (±0.25)
PVC-Exposed	0.41 (±.063)	11.59 (±1.97)	1.20	4.13	0.72 (±0.23)	50 (± 9)	4.27 (±0.29)

NOTE: Numbers within parentheses refer to standard deviation.

*Significantly different from control. + Values represent mean of pooled samples from six rats.

for exactly 1 hr. They were then sacrificed by intraperitoneal pentobarbitone injection, a blood sample was then removed from the hepatic portal vein, and the lungs perfused via the heart with 0.15 *M* NaCl to remove blood from the vascular bed. The lungs were removed from the pleural cavity and lavaged six times with 0.15 *M* NaCl, after which they were dried between paper towels and weighed. The lavaged lung tissue and pooled washes were kept on ice prior to further treatment (see below). Other tissues taken for examination were the liver, spleen, kidney and sections of the gastrointestinal tract which were stored frozen until required.

Fractionation of lavage fluid and biochemical analysis. The free cell population from each animal lavage was obtained by centrifugation at 300 *g* for 20 min at 4°C. The supernatant fraction from six rats in each group was pooled and centrifuged at 1000 *g* for 1 hr at 4°C. The supernatant fraction from this centrifugation contained the majority of soluble alveolar lavage protein.[8] The pellet was resuspended in 4 *M* NaCl, mixed well, and centrifuged at 1500 *g* for 25 min at 4°C, and the resulting separation gave a pellicle of lipoprotein-rich material, designated pulmonary surfactant, which floated to the top of the tube. This was collected, dialyzed against distilled water, freeze-dried, and weighed.[9] The free cell population was counted and the levels of acid RNAase and acid protease were determined as described previously.[9] The incorporation of [^{3}H]-thymidine into tissue DNA and [^{14}C]-proline into tissue protein was determined as follows. Body tissues were homogenized in 0.15 *M* NaCl and samples suspended in a final concentration of 0.2 *M* perchloric acid (PCA) for 1 hr. The mixture was centrifuged at 1000 *g* for 20 min. and the supernatant, containing free label, discarded. This procedure was repeated once more and the resulting pellet was then resuspended in 0.5 *M* PCA at 70°C for 20 min. to solubilize the DNA. The supernatant derived from centrifuging this mixture at 1000 *g* for 20 min. was stored and the process repeated. The supernatant fractions were pooled and samples taken for chemical analysis of DNA and direct counting of [^{3}H] label. The remaining pellet was suspended in distilled water and samples digested in 1 *M* NaOH to assay for protein content or taken up in Soluene for determination of [^{14}C] radiolabel. The efficiency of counting was determined by using internal standards and results were expressed as disintegration per minute of incorporated radiolabel per mg DNA or protein for each tissue examined.

Histopathology. The trachea and lungs from four control and four PVC-exposed rats were removed after the rats had been killed by exsanguination under deep pentobarbitone anaesthesia. The lungs were infused to constant pressure (10 cm water) with buffered 10% formalin, and

^{3}[H]-Thymidine in Lung DNA dpm × 10^{-3}/mg DNA	Protein mg/g Lung	^{14}[C]-Proline in Lung Protein dpm/mg Protein
7.5 (± 4.5)	50.6 (± 8.52)	164 (±55)
10.4 (± 3.6)	52.0 (± 7.46)	165 (±47)
40.0 (±48.0)	77.3 (±19.72)	160 (±23)
25.6 (±14.2)	87.7 (±10.68)	120 (±23)*
14.3 (± 6.9)	70.9 (±10.50)	156 (±20)
10.3 (± 2.3)	77.5 (± 4.14)	165 (±21)
7.7 (± 2.4)	80.5 (± 6.84)	94 (±33)
7.5 (± 1.9)	91.2 (±11.58)	74 (± 6)

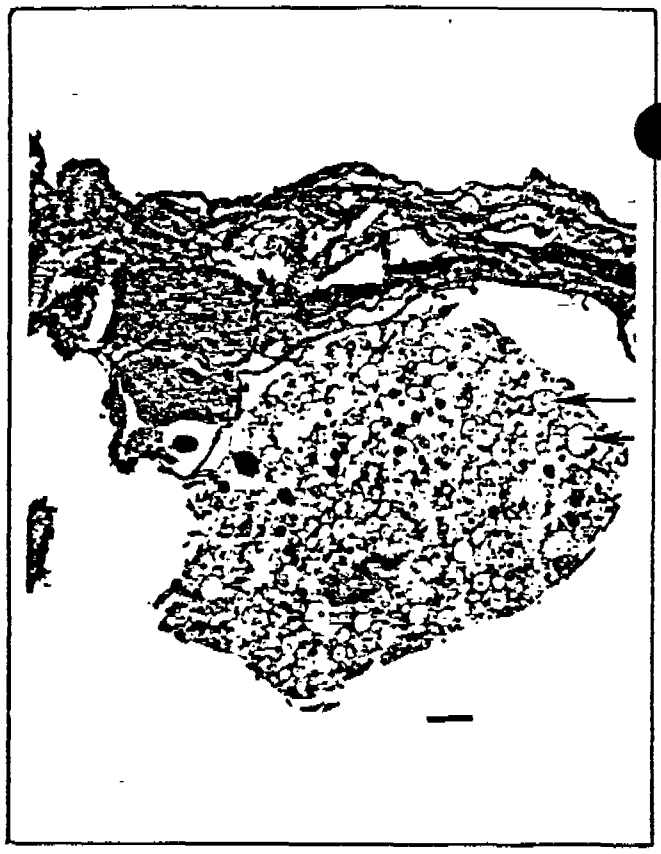

Fig. 1. Lung from rat exposed to PVC dust for 3 wk. Transmission electron microscopy of alveolar macrophage containing numerous smooth-surfaced particles (*arrows*) identical to the inhaled PVC d (scale unit = 2 μm).

transverse sections prepared from embedded material. Sections were stained with hematoxylin/eosin, Masson's trichrome stain for collagen,[10] silver stain for reticular fibers,[11] and with modified Sudan IV to identify PVC particles.[12] Some material was also processed for electron microscopy.

RESULTS

Body weight and clinical signs. There was no effect on body weight of PVC-exposed rats nor any clinical signs that could be related to PVC exposure during the study.

Chamber aerosol analyses. The chamber aerosol was maintained at an average concentration of 10.6 mg/m^3 [standard deviation (*SD*) = 2.3, *N* = 146]. The highest and lowest concentration recorded was 15 mg/m^3 and 7 mg/m^3, respectively. The mass median aerodynamic diameter of the aerosol was 1.7 μm (σg 4.64).

Biochemical studies. Very few significant changes in lung weight/body weight ratio, pulmonary surfactant and alveolar surface protein, free cell number and enzyme activities or lung enzyme activities, protein and DNA 'synthesis' were detected in animals exposed to PVC dust throughout this study (Table 1). In addition, DNA and protein 'synthesis' in the liver, spleen, and kidney, together with changes in acid protease levels in the free cells and lavaged lung tissue, were not detected in PVC-exposed rats (data not shown). Three significant changes in rats exposed to PVC were found: (1) elevated pulmonary surfactant, (2) depressed lung protein 'synthesis' at 9 wk, (3) elevated lung acid RNAase activity at 15 wk.

Histopathology. At 3 wk the lungs of both control and PVC-exposed rats appeared normal, except that in the exposed group the alveolar macrophages were enlarged and contained numerous, 1-4 μm diameter, smooth-surfaced particles similar in appearance to PVC dust (Fig. 1). At 9 wk there was evidence of a mild respiratory tract infection in both control and PVC-exposed groups characterized by increased numbers of mononuclear cells in the perivascular spaces, and in most animals, an increase in the volume and extent of bronchus-associated lymphatic tissue. The foamy macrophages seen at 3 wk in PVC-exposed animals were less evident, possibly because of an increased turnover of cells in the 9-wk group. At 15 wk there was no sign of the respiratory tract infection seen in the rats at 9 wk. In the PVC-exposed animals there were aggregates of foamy macrophages occupying groups of up to 9 alveoli; also associated with these aggregates was hypercellularity due to an increase in mononuclear cells and fibroblasts, in the interstitium of the alveolar wall (Fig. 2). This interstitial reaction was also associated with minima increase in collagen and reticular fibers. The smooth-

Fig. 2. Lung from rat exposed to PVC dust for 15 wk. Note aggregation of foamy macrophages and hypercellularity of adjacent alveolar wall (*arrows*). Hematoxylin and eosin stain (X 250).

surfaced particles that filled foamy macrophages stained red with modified Sudan IV, indicating that they were PVC dust.[12] Fifteen weeks after the final exposure (30 wk from commencement of the experiment), the lungs of control animals appeared normal, while those previously exposed to PVC showed no significant change in the lesions detected at 15 wk (termination of exposure).

DISCUSSION

The results show that a paste polymer preparation of PVC dust inhaled by rats at "nuisance" dust level (10 mg/m^3) for 6 hr/day, 5 days/wk, produces small, randomly scattered, lung lesions after 15 wk of exposure. These lesions are characterized by hypercellularity of the interstitium of the alveolar walls in areas adjacent to macrophage aggregates containing PVC. In addition, the lesions persist 15 wk after the cessation of animal exposure to the particulate. The PVC-induced lesions, however, show only minimal increase in collagen and reticular fiber formation, with no evidence of extensive fibrotic reaction. Similar conclusions are reported by other investigators[5] who studied the effects of intratracheal instillations of different PVC formulations.

The results of the current histopathological study therefore suggest that at "nuisance" dust level PVC has a relatively weak biological reactivity, and this conclusion receives further support from the biochemical investigation. While PVC-exposed animals have elevated levels of pulmonary surfactant and show a decrease in lung protein 'synthesis' 9 wk after exposure, the presence of a mild respiratory tract infection in all the animals during this time period prevents the establishment of any definite conclusions. Thus relatively few, if any, biochemical changes in PVC-exposed rats are detected at any exposure period—either at the alveolar surface, the lung tissue, or other body

organs. Such results are in contrast to previous inhalation studies where rats exposed to 12 mg/m^3 chrysotile asbestos for 5 days/wk for 15 wk have elevated free cell numbers (2-3 X control animals) free cell and lung enzyme activity (3-10 and 1-8 X control, respectively), and pulmonary surfactant (12 X control).[9] Elevations in pulmonary surfactant and free cell numbers are also detected in rats inhaling amosite asbestos and fiber glass (12 mg/m^3, 5 days/wk, for 8 wk).[13] With dusts of "high" biological reactivity these biochemical changes at the lung surface persist with the progressive pathological development of lung disease.

In summary, the present short-term study indicates that at "nuisance" dust level one form of paste polymer PVC has a weak biological reactivity, only detectable by histopathological examination, which reveals a small number of lung lesions in experimental animals. It is not possible at this time to interpret this finding in terms of the lesion likely to arise in man under similar conditions of exposure.

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PVC DUST

Geoff Pigott of CTL has kept in touch with this work at Cardiff. The PVC materials were supplied by ICI and BP under CIA code numbers so anonymously that I have no idea whether PVC 7 came from ICI or BP. Perhaps Dr Tester could disentangle this for us?

J Stafford

JS/SEW/DSO-16
23 June 1981