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PERSPECTIVES

Volume 41, October 1981

POLYVINYL CHLORIDE

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Print Schedule: Volume 42 will present the proceedings from the Symposium on Environmental Epidemiology

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Conference to Reevaluate the Toxicity of Vinyl Chloride Monomer, Poly(vinyl Chloride) and Structural Analogs

National Institutes of Health, Bethesda, MD
March 20-21, 1980

Sponsored by
National Institute of Environmental Health Sciences,
National Institute for Occupational Safety and Health
and
Occupational Safety and Health Administration

Environmental Health Perspectives
Vol. 41, p. 1, 1981

Introduction

It has been over 30 years since the first suggestive evidence was published by Tribukh to indicate that vinyl chloride monomer (VCM) is acutely toxic in man. Chronic toxicity in animals was subsequently demonstrated by Torkelson in 1961, but it was an outbreak to VCM-induced acroosteolysis in the 1960's that focused attention for the first time on the occupational toxicity of this important industrial chemical. The carcinogenicity of VCM was recognized in 1974 following the nearly simultaneous reports of an association between exposure to VCM and angiosarcoma of the liver (ASL) in man (reported by Creech and Johnson) and in animals (reported by Maltoni). These reports precipitated a thorough international review of the toxicity of VCM at the New York Academy of Sciences. Since then, enormous research efforts have been undertaken to expand our knowledge of the toxicity of vinyl chloride. Many of the research efforts stimulated by the events of the 1970's have now come to fruition, and are appropriately brought together in these proceedings.

The proceedings begin with a presentation of the most extensive animal research on the carcinogenicity of VCM ever published. In these data, dose-response curves can be examined by site and type of tumor, by route and schedule of exposure, and by species and strain of animal. This study and other research on the carcinogenicity of VCM reported in this volume indicate the importance of cofactors such as age at exposure and simultaneous exposure to ethyl alcohol in VCM toxicity. Evidence that even a single exposure to VCM induces experimental neoplasia is significant from the standpoint of both occupational and nonoccupational exposures.

The updated epidemiologic studies presented in this volume of mortality among workers exposed to vinyl chloride reinforce the laboratory findings of multisite carcinogenicity. Data demonstrating the mutagenic and transplacental effects of VCM are also updated and summarized. The lack of predictivity of one prospective liver screening program suggests the need for further work in identifying effective medical surveillance techniques for early recognition of liver abnormalities.

While thousands of workers are exposed to VCM vapor, many more are exposed to its polymer, poly(vinyl chloride) (PVC). The carcinogenicity of PVC dust is evaluated both experimentally and epidemiologically in these proceedings. The results are not definitive. Nonmalignant respiratory system effects from PVC dust are suggested by a number of papers at this conference.

Finally, the extension of the findings of carcinogenicity of VCM to its structural analogs, vinylidene chloride, trichloroethylene and tetrachloroethylene, and its brominated equivalent, vinyl bromide, serves as another lead in our effort to understand some fundamental concepts of chemical carcinogenesis.

Richard J. Waxweiler
Philip J. Landrigan
Peter Infante
Raymond Shapiro

Environmental Health Perspectives
Vol. 41, pp. 3-29, 1981

Carcinogenicity Bioassays of Vinyl Chloride Monomer: A Model of Risk Assessment on an Experimental Basis

by Cesare Maltoni,* Giuseppe Lefemine,* Adriano Ciliberti,* Giuliano Cotti* and Donata Carretti*

Data are presented regarding the final results of the Bentivoglio (Bologna) project on long-term carcinogenicity bioassays of vinyl chloride (VC).

The experimental project studied the effects of the monomer, administered by different routes, concentrations and schedules of treatment, to animals (near 7000) of different species, strains, sex and age. To our knowledge this is the largest experimental carcinogenicity study performed on a single compound by a single institution.

The results indicate that VC is a multipotential carcinogen, affecting a variety of organs and tissues. In the experimental conditions studied, the neoplastic effects of the monomer were also detected at low doses. The experimental and biological factors greatly affect the neoplastic response to VC. Long-term carcinogenicity bioassays are, at present, a unique tool for the identification and quantification of environmental and occupational risks. Precise and highly standardized experimental procedures are needed to obtain data for risk assessment.

Introduction

The present report deals with the presentation of the final results of our project on the long-term carcinogenicity bioassays of vinyl chloride (VC) (BT project).

To our knowledge this project is the most extensive experimental carcinogenesis study ever performed on one industrial compound by a single institution.

Planning, Materials, Methods and Performance of the Experiment

Planning

The experiments of the project were planned (a) to test the carcinogenicity of the compound; (b) to obtain information on the site and type of tumors; (c) to evaluate the possible effects of the routes of administration, with particular regard to the ones reproducing potential human exposure; (d) to assess, in quantitative terms, the level of risk. The planning of the experiments was aimed at achieving these goals.

The compound was tested on animals of different species, strain, sex and age (Table 1), since it is known that these factors may modify the neoplastic response qualitatively and quantitatively. The choice of the animals was made with the intention of having an integrated system of complementary biological models which could express a range, as wide as possible, of neoplastic responses.

VC was administered by different routes: intraperitoneal (IP) injection, subcutaneous (SC) injection, inhalation and ingestion (by stomach tube), the latter two being the major routes of potential human exposure.

The monomer was administered at different concentrations: 14 by inhalation levels and 6 ingestion levels for various periods of time, by continuous or intermittent treatment (Table 2).

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Table 1. BT project on VC: animals used.

Species	Strain	Sex	Age
Rat	Sprague-Dawley	M, F	Adult (10–21 wk) Newborn (1 day) Embryo (12 days pregnancy)
Rat	Wistar	M	Adult
Mouse	Swiss	M, F	Adult
Hamster	Golden	M	Adult

The plan of the project is presented in Tables 3-9.

Material

VC was supplied from the same source in all cases, and it contained very low amounts of impurities (Table 10). The oil employed as a vehicle in the ingestion and injection experiments was pure virgin olive oil from Tuscany.

The animals (except for the golden hamsters) were breeds which have been routinely employed in our laboratory for many years. It should be pointed out that, whatever their use, all the animals of our colony undergo periodic examination and complete autopsy, giving us extensive information concerning their pathology.

The chambers for inhalation exposure were built basically of stainless steel and glass.

For the ingestion treatment glass syringes and stainless steel needles with round tips were used.

To control the level of exposure in the inhalation experiments, an automatic gas chromatography system was used.

Table 2. BT project on VC: routes, concentrations and schedules.

Route	Concentration	Schedule
Inhalation	30,000, 10,000, 6000, 2500, 500, 250, 200, 150, 100, 50, 25, 10, 5, 1 ppm	4 hr/day, 5 days/wk, 52 wk
	10,000, 6000, 2500, 500, 250, 50 ppm	4 hr/day, 5 days/wk, 17 wk
	10,000, 6000 ppm	4 hr/day, 5 days/wk, 5 wk
	10,000, 6000 ppm	4 hr/day, 1 day/wk, 25 wk
	10,000, 6000 ppm	1 hr/day, 4 days/wk, 25 wk
	10,000, 6000 ppm	4 hr/day, 7 days
Ingestion	50, 16.65, 3.33, 1.0, 0.3, 0.03, mg/kg body weight	5 times/wk, 52 wk
IP injection	4.25 mg	4, 3, or 2 times at 2 month intervals
	4.25 mg	Once only
SC injection	4.25 mg	Once only

Table 3. Plan of long-term experiments on the effects of exposure by inhalation for 1 year to different doses of VC on adult Sprague-Dawley rats (basic experiments).

Expt. no.	Treatment: Route	Treatment: VC dose	Treatment: Duration	Animals: Species	Animals: Strain	Animals: Age, weeks	Animals: No. ♀	Animals: No. ♂	Animals: Total	Animals: No. per group
BT1	Inhalation	10,000, 6000, 2500, 500 250, 50 ppm Untreated controls Treated controls VA, 2500 ppm	4 hr/day, 5 days/wk, 52 wk	Rat	Sprague-Dawley	13	240	240	480	60
BT2	Inhalation	200, 150, 100 ppm Untreated controls	4 hr/day, 5 days/wk, 52 wk	Rat	Sprague-Dawley	13	280	265	545	120–185
BT6	Inhalation	30,000 ppm	4 hr/day, 5 days/wk, 52 wk	Rat	Sprague-Dawley	17	30	30	60	60
BT9	Inhalation	50 ppm Untreated controls	4 hr/day, 5 days/wk, 52 wk	Rat	Sprague-Dawley	11	200	200	400	100 (c) 300 (t)
BT15	Inhalation	25, 10, 5, 1 ppm Untreated controls	4 hr/day, 5 days/wk, 52 wk	Rat	Sprague-Dawley	13	300	300	600	120

Table 4. Plan of long-term experiments on the effects of length of VC exposure on VC carcinogenicity.

Expt. no.	Treatment			Animals						
	Route	VC dose	Duration	Species	Strain	Age, weeks	No. ♀	No. ♂	Total	No. per group
BT3	Inhalation	10,000, 6000, 2500, 500, 250, 50 ppm Untreated controls	4 hr/day, 5 days/wk, 17 wk	Rat	Sprague-Dawley	12	262	288	550	60–190
BT10	Inhalation	10,000, 6000, ppm Untreated controls	4 hr/day, 5 days/wk, 5 wk; 4 hr/day, 1 day/wk, 25 wk; 1 hr/day, 4 days/wk, 25 wk	Rat	Sprague-Dawley	11	420	420	840	120

Table 5. Plan of long-term experiments on the effects of age on vinyl chloride carcinogenicity.

Expt. no.	Treatment			Animals						
	Route	VC dose	Duration	Species	Strain	Age, weeks	No. ♀	No. ♂	Total	No. per group
BT5	Transplacental	10,000, 6000 ppm	4 hr/day, 7 days (from 12th to 18th day of pregnancy)	Rat	Sprague-Dawley	19 (breeders) 12 days (embryos)	110	36	146	30–54
BT14	Inhalation	10,000, 6000 ppm	4 hr/day, 5 days/wk, 5 wk	Rat	Sprague-Dawley	1 day	45	44	89	43–46

Table 6. Plan of long-term experiments on the effects of strain on vinyl chloride carcinogenicity.

Expt. no.	Treatment			Animals						
	Route	VC dose	Duration	Species	Strain	Age, weeks	No. ♀	No. ♂	Total	No. per group
BT7	Inhalation	10,000, 6000, 2500, 500, 250, 50 ppm Untreated controls	4 hr/day, 5 days/wk, 52 wk	Rat	Wistar	11	0	220	220	30–40
BT17	Inhalation	1 ppm Untreated controls	4 hr/day, 5 days/wk, 52 wk	Rat	Wistar	13	0	250	250	120–130

Table 7. Plan of long-term experiments on the effects of species on vinyl chloride carcinogenicity.

Expt. no.	Treatment			Animals						
	Route	VC dose	Duration	Species	Strain	Age, weeks	No. ♀	No. ♂	Total	No. per group
BT4	Inhalation	10,000, 6000, 2500, 250, 50 ppm Untreated controls	4 hr/day, 5 days/wk, 30 wk	Mouse	Swiss	11	500, 250	260	510	60–150
BT8	Inhalation	10,000, 6000, 2500, 500, 250, 50 ppm Untreated controls	4 hr/day, 5 days/wk, 30 wk	Hamster	Golden	11	10	268	268	30–62

Table 8. Plan of long-term ingestion experiments on vinyl chloride carcinogenicity.

Expt. no.	Treatment: Route	VC dose	Duration	Animals: Species	Strain	Age, weeks	No. ♀	No. ♂	Total	No. per group
BT11	Ingestion	50, 16.65, 3.33 mg/kg body weight in olive oil Controls, olive oil	5 times/wk, 52 wk	Rat	Sprague-Dawley	13	160	160	320	80
BT27	Ingestion	1, 0.3, 0.03 mg/kg body weight in olive oil Controls, olive oil	5 times/wk, 52 wk or 59 wk[a]	Rat	Sprague-Dawley	10	300	300	600	150

[a]For 10 animals of each of the three exposed and control groups the treatment was planned to last 104 weeks, but it had to be stopped because of animal intolerance.

Table 9. Plan of long-term injection experiments on vinyl chloride carcinogenicity.

Expt. no.	Treatment: Route	VC dose	Duration	Animals: Species	Strain	Age, weeks	No. ♀	No. ♂	Total	No. per group
BT12	IP injection	4.25 mg in 1.0 cc olive oil Controls, 1.0 cc olive oil	4, 3, 2, or 1 times; two month intervals	Rat	Sprague-Dawley	13	150	150	300	60
BT13	SC injection	4.25 mg in 1.0 cc olive oil Controls, 1.0 cc olive oil	1 injection	Rat	Sprague-Dawley	21	80	70	150	75

Table 10. Maximum level of impurities in the VC used.

Impurity	Concn, ppm
H_2O	10
Acetic aldehyde	5
Acetylene	2
Allene	5
Butane	8
1,3-Butadiene	10
Chlorophene	10
Diacetylene	4
Vinyl acetylene	10
Propine	8
Methyl chloride	100

Methods and Procedures

For the experiment on VC, as well as for any other long-term experimental bioassays performed in our laboratory, the procedure has been always the same highly standardized and controlled one. In particular, the following points in our laboratory standard procedures, should be emphasized.

Compounds. All shipments of VC used were examined in order to determine whether they meet the required standards.

Concentrations. The concentrations, particularly when VC was given by inhalation, were controlled by continuous gas chromatographic monitoring.

Modalities of Treatment. Treatment was always performed by the same people. This is particularly important for gavage, since the animals become accustomed to the same operator.

Control of the Animals. The conditions of the animals was checked three times daily. Every two weeks the animals were examined to detect any gross changes.

Weight of the Animals. The animals were weighed every two weeks during treatment and every eight weeks after the end of treatment.

Duration of the Experiments. In the VC project, as in any other long-term bioassays performed in our laboratory, the animals were kept alive until spontaneous death.

Autopsy. Full autopsy was performed on each animal. All parts of the body were explored, including the central nervous system. Specimens for histology included the brain, Zymbal glands, interscapular brown fat, salivary glands, tongue, lungs, liver, kidneys, adrenals, spleen, pancreas, stomach, intestine, bladder, uterus, gonads and any other organ with pathological lesions.

Histology. Specimens were trimmed in the standard way. Sections were routinely stained with Haematoxylin-Eosin and, when necessary, with special techniques.

Histopathological Examination. All sides were screened by a junior pathologist and then reviewed

by a senior pathologist. The same classification of the lesions were used by all pathologists.

Classification of Data. All the anatomical sites and the gross and microscopic observations were classified and coded following our laboratory codes (Tables 11-13).

Table 11. Codes of organs considered (sequence).

Code	Organ	Code	Organ
1	Skin (epidermis and dermis)	32	Adrenals
2	Epidermal appendages	33	Cerebrum
3	Zymbal glands	34	Cerebellum
4	Subcutaneous tissues	35	Spinal marrow
5	Mammary glands	36	Peripheral nervous system: ganglia
6	Parotid glands	37	Peripheral nervous system: nerves
7	Submaxillary glands	38	Eyes
8	Nasal and paranasal cavities	39	Harderian glands
9	Oral cavity	40	Skeletal muscles (diaphragm not included)
10	Tongue	41	Diaphragm
11	Lung	42	Bones
12	Pleura and pleural cavity	43	Articulations
13	Esophagus	44	Heart
14	Forestomach	45	Pericardium and pericardial cavity
15	Glandular stomach	46	Large vessels
16	Intestine	47	Thymus
17	Liver	48	Spleen
18	Pancreas	49	Axillary and inguinal lymph nodes
19	Peritoneum and peritoneal cavity	50	Head-neck lymph nodes
20	Kidneys	51	Interthoracic and parathymic lymph nodes
21	Pelves	52	Intrabdominal lymph nodes
22	Ureters	53	Lymph nodes of other sites
23	Bladder	54	Bone marrow
24	Ovaries	55	Soft tissues of support
25	Uterus	56	Interscapular fat pad
26	Seminal vesicles	57	Trachea
27	Prostate	58	Ear
28	Testicles	59	Female external sex organs
29	Epididymis	60	Male external sex organs
30	Hypophysis	61	Odontogenic apparatus
31	Thyroid	62	Gall bladder

Table 12. Codes of macroscopic changes.

Code	Change	Code	Change
1	No change	19	Dilatation of organ with cavity
2	Alopecia	20	Protrusion of eyeball
3	Keratosis	21	Simple cyst
4	Degenerative pathosis	22	Hemorrhagic cyst
5	Ulceration	23	Multiple simple cyst
6	Hyperemia, edema and hemorrhage	24	Multiple hemorrhagic cyst
7	Phlogosis (including of abscess)	25	Polypoid formation
8	Pulmonary hepatization	26	Papillomatous formation and horn
9	Pulmonary emphysema	27	Solid nodule
10	Irregular surface	28	Hemorrhagic nodule
11	Granulations and plaques	29	Cystic mass
12	Simple thickening	30	Solid mass
13	Thickening of capsule	31	Solid necrotic mass
14	Fibrosis	32	Hemorrhagic mass
15	*In toto* reduction	33	Ossifying mass
16	Atrophy	34	Serous effusion
17	*In toto* enlargement	35	Fibrinous-purulent effusion
18	Augmentation in consistency	36	Hemorrhagic effusion

Table 13. Codes of microscopic changes.

Code	Change	Code	Change
1	No changes	57	Fibroangiomatosis
2	Mild regressive changes	58	Simple polyp
3	Serious regressive changes	59	Polyp with cellular distypias
4	Necrosis	60	Papilloma
5	Ulcer	61	Fibropapilloma
6	Amyloidosis	62	Acanthoma
7	Hyalinosis	63	Trichoepithelioma
8	Colloid-cystic degeneration	64	Simple adenoma
9	Calcifications	65	Muciparous adenoma
10	Emphysema	66	Colloid-cystic adenoma
11	Vascular changes (hyperemia, dilatation of sinusoids and other vessels, edema and hemorrhage)	67	Exocrine pancreas adenoma
12	Hematic cyst	68	Endocrine pancreas adenoma (Islet cell adenoma)
13	Organized fibrinous coagulum	69	Chromophobe adenoma
14	Hemorrhagic effusion	70	Chromophilic adenoma
15	Acute phlogistic changes (including abscess)	71	Cortical adenoma
16	Chronic phlogistic changes (also reactive)	72	Medullary adenoma
17	Particular granulomatous changes	73	Cholangioma
18	Phlogistic effusion	74	Hepatocellular adenoma or hepatoma
19	Thickening of capsule	75	Tumor of granulosa and of theca
20	Thickening of submesothelial tissues	76	Leydig cell tumor
21	Fibrosis	77	Other epithelial benign tumors
22	Post necrotic fibrosis (comprehensive of cirrhosis)	78	Fibroma
23	Fibrous thickening of vessels	79	Mixoma
24	Cystic ectasia of blood vessels with fibrosis	80	Lipoma
25	Cystic ectasia of blood vessels with fibrosis and hyperplasia of perithelial cells	81	Leiomyoma
26	Cystic ectasia of blood vessels with fibrosis and dysplasia of perithelial cells	82	Rhabdomyoma
27	Cellular depletion and atrophy (with or without fibrosis)	83	Chondroma
28	Simple cyst	84	Osteoma
29	Hemorrhagic cyst	85	Angioma
30	Multiple simple cyst	86	Fibroangioma
31	Multiple hemorrhagic cyst	87	Ossifying angioma
32	Dilatation of organs with cavity (including hydronephrosis)	88	Other benign tumors of connective tissue
33	Hyperplasia and squamous metaplasia	89	Fibroadenoma
34	Glandular simple and cystic hyperplasia	90	Adenomyoma
35	Diffused parenchymal hyperplasia	91	Benign tumors of nervous ganglia (ganglioneuroma) and benign sympathetic tumors of adrenal medulla
36	Nodular parenchymal hyperplasia	92	Benign tumors of peripheral nerves (neurilemoma)
37	Cortical hyperplasia	93	Carcinoma
38	Medullary hyperplasia	94	Carcinoma with metastases
39	Hyperplasia of stroma	95	Basocellular carcinoma
40	Reactive hyperplasia	96	Basocellular carcinoma with metastases
41	Simple proliferation of lymphoreticular cells with myelopoiesis	97	Squamocellular carcinoma
42	Proliferation of angioblastic cells	98	Squamocellular carcinoma with metastases
43	Fibroangioblastic proliferation	99	Transitional cell carcinoma
44	Proliferation of lipocytes	100	Transitional cell carcinoma with metastases
45	Proliferation of biliary ducts	101	Adenocarcinoma
46	Proliferation of renal tubules and/or of nephroblastema	102	Adenocarcinoma with metastases
47	Adenomatous hyperplasia	103	Biliary duct adenocarcinoma
48	Cholangiofibrosis	104	Biliary duct adenocarcinoma with metastases
49	Dysplasia (comprehensive of neoplastic parenchymal nodule of liver)	105	Hepatocellular carcinoma or hepatocarcinoma
50	Simple and cystic glandular dysplasia	106	Hepatocarcinoma with metastases
51	Cortical dysplasia	107	Exocrine pancreas adenocarcinoma
52	Medullary dysplasia	108	Exocrine pancreas adenocarcinoma with metastases
53	Dysplasia of angioblastic cells	109	Cortical adenocarcinoma
54	Papillomatosis	110	Cortical adenocarcinoma with metastases
55	Acanthomatosis	111	Pheochromoblastoma
56	Angiomatosis	112	Pheochromoblastoma with metastases
		113	Nephroblastoma
		114	Nephroblastoma with metastases
		115	Seminoma
		116	Seminoma with metastases
		117	Melanoma
		118	Melanoma with metastases
		119	Other malignant epithelial tumors

Table 13. (cont.)

Code	Change	Code	Change
120	Other malignant epithelial tumors with metastases	145	Carcinosarcoma
121	Mesothelioma	146	Carcinosarcoma with metastases
122	Mesothelioma with metastases	147	Neuroblastoma
123	Fibrosarcoma	148	Neuroblastoma with metastases
124	Fibrosarcoma with metastases	149	Glioma (astrocytoma, oligodendroglioma, microglioma)
125	Mixosarcoma	150	Ependymoma
126	Mixosarcoma with metastases	151	Meningioma
127	Liposarcoma	152	Malignant tumors of nervous ganglia and malignant sympathetic tumors of adrenal medulla
128	Liposarcoma with metastases	153	Malignant tumors of nervous ganglia and malignant sympathetic tumors of adrenal medulla with metastases
129	Leiomyosarcoma	154	Malignant tumors of peripheral nerves (malignant schwannoma)
130	Leiomyosarcoma with metastases	155	Malignant tumors of peripheral nerves (malignant schwannoma) with metastases
131	Rhabdomyosarcoma	156	Characteristic tumors of eyes
132	Rhabdomyosarcoma with metastases	157	Lymphoreticular neoplastic localizations
133	Chondrosarcoma	158	Secondary localizations of tumors from other anatomical districts
134	Chondrosarcoma with metastases	159	Neoplastic effusions
135	Osteosarcoma	160	Odontoma
136	Osteosarcoma with metastases	161	Chondromatosis
137	Angiosarcoma	162	Histiocytosis and benign histiocytoma
138	Angiosarcoma with metastases	163	Mesothelial hyperplasia
139	Ossifying angiosarcoma		
140	Ossifying angiosarcoma with metastases		
141	Angiopericytosarcoma		
142	Angiopericytosarcoma with metastases		
143	Other malignant tumors of connective tissue		
144	Other malignant tumors of connective tissue with metastases		

For each animal an individual final card was prepared, which included data on experimental factors, survival, weight at 6, 12, 18 and 24 months, and any gross and microscopic lesions. Samples are shown in Figures 1 and 2.

Presentation of Pathological Data. The results of all VC experiments, as well as those of any other experiment performed in our laboratory, will be presented in the final report (now in press) with the same types of tables, in the same sequence.

This type of presentation has been made possible by the knowledge of the basic pathology of the animal used, which enabled us to make an approximated census of the expected lesions.

Such a procedure permits a quick comparison among the results of different experiments of the same project and possibly of the results of projects studying different compounds.

Interpretation of the Data. The data were submitted to statistical analysis. Although statistical analysis provides an extremely important tool for interpreting the meaning of the results of long-term bioassays, it should be stressed that there may be smaller differences between exposed and control groups which do not reach statistical significance, while these differences could still have meaning from an oncological point of view (particularly in the case of tumors which are infrequent in the animal colony).

Therefore, the most important data should be commented on both in the light of the statistical analysis performed and from a biological point of view.

The methodological protocol adopted meets the requirements of the recent Good Laboratory Practice Act.

Results

Part of these results, namely those dealing with seven basic experiments on the effects of long-term exposure to a range of 14 doses by inhalation (from 30,000 to 1 ppm) and of six doses by ingestion (from 50 mg to 0.03 mg/kg bw), on Sprague-Dawley rates, were presented previously (*1*, *2*).

A report, for limited circulation, dealing with part of the results has also appeared (*3*).

The results of the whole project, with detailed tables, will appear in a monograph which will encompass data on survival rate, body weight, regressive and inflammatory changes, benign and malignant tumors, neoplastic precursors, and the most important proliferative changes.

With this report we are presenting only tables summarizing the most outstanding results and information, and what we do believe to be the integrative documentation and strictly necessary comments.

		Code
Agent: Vinyl chloride		XVIII, 1
Experiment No.: BT 6		
Group No.: I	No. animal: 10	
Type of exposure	Inhalation	I, 1
Concentration: 30,000 ppm		II, 1
Treatment protocol: 4 hr/day, 5 days/ week, 52 weeks		VI, 5
Species: Rat		X, 1
Strain: Sprague-Dawley		XI, 1
Sex: Female		XII, 1
Age at start of experiment (weeks): 17		XIII, 10
Total dose received:		
Age at death (weeks): 85		
Period from start of treatment (weeks): 68		
Weight (g)		
6 months: 247		
12 months: 278		
18 months: 290		
24 months:		

FIGURE 1. Sample treatment protocol card.

Tables 15-31 presented data on the incidence of the tumors which have been considered as dependent or possibly correlated to VC exposure, in 17 different experiments on the effects of VC in different animal systems, by different routes, at different doses and with various schedules of treatment. Explanations of abbreviations used in the tables are given in Table 14.

The possible leukemogenic effect of VC in golden hamsters is expressed both by the slight increase in incidence but more by the decrease in latency time (from 16 weeks in animals treated at 10,000 ppm to 36 weeks in control animals).

Examples of the most characteristic microscopic features of these tumors were given in a previous publication (*4*).

The data on dose-response relationship in long-term treatment experiments, by inhalation and by ingestion, in Sprague-Dawley rats, Wistar rats and Swiss mice, with reference to the incidence of total malignant and benign tumors, and the most important neoplasias observed, are shown in Tables 32-63.

The striking effect of the influence of scheduled treatment is pointed out by the results shown in Table 64.

Examples of the marked influence of the animals used in determining the neoplastic response are shown in Tables 65-67, which point out the effects of species, strain and age.

Conclusions

VC-dependent tumors are identified on the basis of one or more of the following parameters: (a) sharply enhanced incidence; (b) rare or exceptional occurrence in the colony of the animal used; (c) dose-response relationship; (d) association of precursor lesions.

From the presented data the following conclusions may be drawn.

(1) VC causes tumors in all the different animal systems tested.

(2) VC is a multipotential carcinogen, since it causes tumors of different types in different sites (Table 68).

(3) Some types of tumors are observed in all the animals studied, i.e., liver angiosarcoma, whereas others are observed in only one animal system.

(4) The degree of evidence of correlation between VC treatment and the tumors considered as VC-dependent varies from tumor to tumor.

(5) VC shows carinogenic effects both when given by inhalation and ingestion and possibly by injection.

(6) Both through inhalation and ingestion experiments there is a clear-cut dose-response relationship.

(7) The duration of treatment and schedule of treatment greatly affects the neoplastic response.

(8) The neoplastic response, in qualitative and quantitative terms, is greatly affected by the species, the strain and the sex of the animals studied.

(9) Newborn animals appear to be extremely responsive and easily develop liver tumors, both hepatocarcinomas and angiosarcomas.

(10) VC produces carcinogenic effects on embryos via the placenta.

(11) With the above criteria for identifying VC-dependent tumors, VC shows carcinogenic effects even at low doses, namely down to 50 ppm and less.

(12) The results of the seven basic experiments studying the effects of doses of VC as given by inhalation (BT1, 2, 6, 9, 15), and ingestion (BT11, 27), have been subject to statistical analysis following the Fisher exact probability test ($p \leq 0.05$). The total cancer-bearing animals and the tumors

Macroscopic changes:				
Site	*Type*	*Side*	*No.*	*Code*
Subcutaneous tissues	Hemorrhagic nodule		1	4, 28, D1
Lung	Hemorrhagic nodule			11, 28, D12
Pleura and pleural cavity	Hemorrhagic effusion			12, 36
Forestomach	No changes			14, 1
Liver	Hemorrhage			17, 6
Peritoneum and peritoneal cavity	No changes			19, 1
Adrenals	Hemorrhagic mass	Sn	1	32, 32, C1, D1
Harderian glands	No changes	Sn		39, 1, C1
Intrathoracic and parathymic lymph node	In toto enlargement			51, 17

Microscopic changes:				
Site	*Type*	*Side*	*No.*	*Code*
Subcutaneous tissues	Fibroangioma			4, 86
Lung	Secondary neoplastic localization (liver angiosarcoma)			11, 158 (17, 138)
Pleura and pleural cavity	Secondary neoplastic localization (liver angiosarcoma)			12, 158 (17, 138)
Forestomach	Papilloma			14, 60
Liver	Hepatocarcinoma			17, 105
	Angiosarcoma with metastases			17, 138
Peritoneum and peritoneal cavity	Secondary neoplastic localization (liver angiosarcoma)			19, 158 (17, 138)
Adrenals	Cortical adenoma	Sn		32, 71, C1
Harderian glands	Abscess	Sn		39, 15, C1
Intrathoracic and parathymic lymph node	No changes			51, 1

FIGURE 2. Sample record of macroscopic and microscopic changes.

Table 14. Abbreviations used in tables.[a]

Abbreviation	
T	Tumor
Ca	Carcinoma
Ep T	Epithelioma
Pa	Papilloma
Ac	Acanthoma
Ad	Adenoma
Ad †	Adenoma in malignant transformation
MT	Malignant tumors (total if not otherwise specified)
BT	Benign tumors (total if not otherwise specified)
LAS	Liver angiosarcoma
LA	Liver angioma
ELAS	Extra-liver angiosarcoma
ELA	Extra-liver angioma
Nephro-BL	Nephroblastoma
Neuro-BL	Neuroblastoma
A	Angioblastic hyperplasia in liver
A †	Angioblastic dysplasia in liver
Neop. nod.	Neoplastic nodules of liver
Nod. hyp.	Nodular hyperplasia of liver
Dif. hyp.	Diffused hyperplasia of liver
+ +	Marked
+ + +	Very marked

[a]The incidence of total malignant and benign tumours is given as the total number of tumors per 100 animals (one animal may bear more than one malignant or benign tumor) on the basis of the tumors observed among the animals alive, when the first tumor was observed in the experiment.

The incidence of specific tumour is given, as percent of the animals bearing the tumor considered, referred to the animals alive when the first tumor was observed (in parentheses).

significantly in excess in these experiments, in relation to dose, are given in Tables 69 and 70.

The Fisher exact probability test at 95% confidence is, in relation to the above, not "sensitive" enough, in our experimental conditions.

Biologically, in our opinion, the following results, although not statistically significant according to the test used, should be given proper attention.

Extrahepatic angiosarcomas of different sites are observed at a very low incidence dose in untreated Sprague-Dawley rats of our colony. Results of experiments BT1 and particularly BT9, however, strongly suggest a relationship between these tumors and VC exposure. This relationship is supported by the excessive incidence of extrahepatic vascular tumors in mice treated with VC (BT4).

Few cases of hepatomas have been observed in treated groups, particularly in BT1. This tumor is exceptionally rare in our colony of animals, and none have been observed in the control group of the 17 experiments. Moreover the relationship with treatment is supported by the fact that a high incidence of hepatomas has been observed in Sprague-Dawley rats, following neonatal exposure to a high dose for a short period (BT14).

In view of their rareness or nonobservation in the colony of animal used, for the following tumors it should be stressed that attention should be paid to

Table 15. Experiment BT1.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac	Mammary MT
I 10,000 ppm	81.7	23.3	11.7 (7/60)	–	5.0 (3/60)	5.0 (3/60)	1.7 (1/60)	8.3 (5/60)	11.7 (7/60)	26.7 (16/60)	5.0 (3/60)	–	5.0 (3/60)
II 6000 ppm	60.0	38.3	22.0 (13/59)	3.4 (2/59)	5.1 (3/59)	6.8 (4/59)	1.7 (1/59)	8.5 (5/59)	5.1 (3/59)	11.9 (7/59)	3.4 (2/59)	1.7 (1/59)	–
III 2500 ppm	63.3	20.0	21.7 (13/60)	–	5.0 (3/60)	3.3 (2/60)	3.3 (2/60)	10.0 (6/60)	6.7 (4/60)	3.3 (2/60)	1.7 (1/60)	–	3.3 (2/60)
IV 500 ppm	51.7	13.3	10.0 (6/60)	–	1.7 (1/60)	1.7 (1/60)	8.3 (5/60)	10.0 (6/60)	–	6.7 (4/60)	1.7 (1/60)	–	1.7 (1/60)
V 250 ppm	30.0	25.0	5.1 (3/59)	1.7 (1/59)	3.4 (2/59)	–	1.7 (1/59)	8.5 (5/59)	–	–	3.4 (2/59)	–	3 4 (2/59)
VI 50 ppm	15.0	36.7	1.7 (1/60)	–	1.7 (1/60)	3.3 (2/60)	–	1.7 (1/60)	–	–	1.7 (1/60)	1.7 (1/60)	3.3 (2 60)
VII No treatment (control)	13.3	43.3	–	–	–	3.4 (2/58)	–	–	–	–	1.7 (1/58)	–	–

[a]Exposure by inhalation to VC in air at 10,000, 6000, 2500, 500, 250, and 50 ppm; 4 hr/day, 5 days/week, for 52 weeks. Sprague-Dawley rats, M and F, 13 weeks old. Results after 135 weeks (end of experiment).

Table 16. Experiment BT2.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac	Mammary MT
I 200 ppm	35.0	21.7	10.0 (12/120)	3.3 (4/120)	0.8 (1/120)	0.8 (1/120)	2.5 (3/120)	5.8 (7/120)	–	3.3 (4/120)	4.2 (5/120)	–	5.0 (6 120)
II 150 ppm	35.0	25.0	5.0 (6/119)	–	–	0.8 (1/119)	–	9.2 (11/119)	–	3.4 (4/119)	3.4 (4/119)	1.7 (2/119)	5.0 (6 119)
III 100 ppm	21.7	27.5	0.8 (1/120)	0.8 (1/120)	–	–	–	8.3 (10/120)	–	0.8 (1/120)	0.8 (1/120)	3.8 (4/120)	3.3 (4 120)
IV No treatment (control)	15.7	21.6	–	–	1.1 (2/185)	–	–	–	–	1.1 (2/185)	1.1 (2/185)	1.6 (3/185)	1.0 (2 185)

[a]Exposure by inhalation to VC in air at 200, 150, 100 ppm; 4 hr/day, 5 days/week, for 52 weeks. Sprague-Dawley rats, M and F, 13 weeks old. Results after 143 weeks (end of experiment).

Table 17. Experiment BT6.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac	Mammary MT
I 30,000 ppm	100.0	50.0	30.0 (18/60)	1.7 (1/60)	1.7 (1/60)	5.0 (3/60)	1.7 (1/60)	–	1.7 (1/60)	58.3 (35/60)	1.7 (1/60)	18.3 (11/60)	3.3 (2 60)

[a]Exposure by inhalation to VC in air at 30,000 ppm; 4 hr/day, 5 days/week, for 52 weeks. Sprague-Dawley rats, M and F, 17 weeks old. Results after 68 weeks (end of experiment).

Table 18. Experiment BT9.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac	Mammary MT
I 50 ppm	44.3	41.7	4.8 (14/294)	2.7 (8/294)	3.1 (9/294)	3.7 (11/294)	-	0.3 (1/294)	-	3.1 (9/294)	1.0 (3/294)	0.4 (1/294)	21.7 (62/294)
II No treatment (control)	23.0	24.0	-	-	-	-	-	-	-	-	-	1.0 (1/98)	10.2 (10/98)

[a]Exposure by inhalation to VC in air at 50 ppm; 4 hr/day, 5 days/week, for 52 weeks. Sprague-Dawley rats, M and F, 13 weeks old. Results after 142 weeks (end of experiment).

Table 19. Experiment BT15.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac	Mammary MT
I 25 ppm	33.3	58.3	4.2 (5/120)	0.8 (1/120)	-	2.5 (3/120)	-	0.8 (1/120)	-	3.3 (4/120)	-	-	15.0 (17/120)
II 10 ppm	31.7	53.3	0.8 (1/119)	-	1.7 (2/119)	2.5 (3/119)	-	-	-	1.7 (2/119)	-	-	17.6 (21/119)
III 5 ppm	35.8	55.0	-	-	-	-	-	-	-	0.8 (1/119)	0.8 (1/119)	-	18.5 (22/119)
IV 1 ppm	22.5	44.2	-	-	-	-	-	-	-	0.8 (1/118)	0.8 (1/118)	-	12.7 (15/118)
V No treatment (control)	23.3	37.5	-	-	-	0.8 (1/120)	-	-	-	1.7 (2/120)	-	-	5.8 (7/120)

[a]Exposure by inhalation to VC in air at 25, 10, 5, 1 ppm; 4 hr/day, 5 days/week, for 52 weeks. Sprague-Dawley rats, M and F, 13 weeks old. Results after 147 weeks (end of experiment).

Table 20. Experiment BT3.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac	Mammary MT
I 10,000 ppm	45.0	20.0	-	-	-	1.7 (1/58)	1.7 (1/58)	1.7 (1/58)	15.5 (9/58)	15.5 (9/58)	8.6 (5/58)	1.7 (1/58)	1.7 (1/58)
II 6000 ppm	53.3	25.0	1.7 (1/60)	-	-	3.3 (2/60)	1.7 (1/60)	1.7 (1/60)	20.0 (12/60)	15.0 (9/60)	8.3 (5/60)	3.3 (2/60)	1.7 (1/60)
III 2500 ppm	41.7	35.0	1.7 (1/60)	-	-	-	3.3 (2/60)	3.3 (2/60)	8.3 (5/60)	11.7 (7/60)	3.3 (2/60)	-	6.7 (4/60)
IV 500 ppm	15.0	35.0	1.7 (1/60)	-	-	-	-	-	-	1.7 (1/60)	-	-	5.0 (3/60)
V 250 ppm	21.7	25.0	-	1.7 (1/59)	-	1.7 (1/59)	-	10.2 (6/59)	-	1.7 (1/59)	-	5.1 (3/59)	1.7 (1/59)
VI 50 ppm	18.3	25.0	-	1.7 (1/58)	-	1.7 (1/58)	-	5.2 (3/58)	-	-	1.7 (1/58)	-	1.7 (1/58)
VII No treatment (control)	14.7	20.0	-	-	0.5 (1/190)	-	-	-	-	1.0 (2/190)	0.5 (1/190)	-	2.6 (5/190)

[a]Exposure by inhalation to VC in air at 10,000, 6000, 2500, 500, 250, and 50 ppm; 4 hr/day, 5 days/week, for 17 weeks. Sprague-Dawley rats, M and F, 12 weeks old. Results after 156 weeks (end of experiment).

Table 21. Experiment BT10.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac	Mammary MT
I 10,000 ppm	33.3	41.7	0.8 (1/118)	–	–	0.8 (1/118)	0.8 (1/118)	–	–	7.6 (9/118)	–	2.5 (3/118)	11.0 (13/118)
II 6000 ppm	30.0	45.0	–	0.8 (1/120)	–	1.7 (2/120)	–	0.8 (1/120)	0.8 (1/120)	7.5 (9/120)	–	1.7 (2/120)	10.8 (13/120)
III 10,000 ppm	35.8	45.0	0.8 (1/119)	1.7 (2/119)	–	0.8 (1/119)	–	–	–	7.6 (9/119)	2.5 (3/119)	2.5 (3/119)	13.4 (16/119)
IV 6000 ppm	30.8	39.2	2.5 (3/118)	–	1.7 (2/118)	–	–	–	–	4.2 (5/118)	3.4 (4/118)	1.7 (2/118)	9.3 (11/118)
V 10,000 ppm	41.7	45.0	0.8 (1/119)	1.7 (2/119)	–	0.8 (1/119)	–	0.8 (1/119)	0.8 (1/119)	6.7 (8/119)	0.8 (1/119)	0.8 (1/119)	16.8 (20/119)
VI 6000 ppm	33.3	50.8	0.8 (1/120)	1.7 (2/120)	0.8 (1/120)	–	1.7 (2/120)	0.8 (1/120)	–	7.5 (9/120)	–	0.8 (1/120)	10.0 (12/120)
VII No treatment (control)	16.6	41.0	–	–	–	0.4 (1/227)	–	–	–	–	0.9 (2/227)	2.2 (5/227)	7.5 (17/227)

[a]Exposure by inhalation to VC in air at 10,000, 6000, ppm; 4 hr/day, 5 days/week, for 5 weeks (groups I and II) or 1 hr/day, 4 days/week, for 25 weeks (groups III and IV) or 4 hr/day, once weekly, for 25 weeks (groups V and VI) (100 hr). Sprague-Dawley rats, M and F, 13 weeks old. Results after 154 weeks (end of experiment).

Table 22. Experiment BT5.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac	Mammary MT
I 10,000 ppm	6.7	36.7	–	–	–	–	–	–	–	3.3 (1/30)	–	–	–
II 6000 ppm	6.7	23.3	–	–	–	–	–	–	–	–	–	–	–
III 10,000 ppm	29.6	22.2	–	–	–	–	–	5.9 (3/51)	–	9.8 (5/51)	–	2.0 (1/51)	2.0 (1/51)
IV 6000 ppm	21.9	46.9	–	–	–	3.1 (1/32)	–	–	–	9.4 (3/32)	3.1 (1/32)	3.1 (1/32)	6.2 (2/32)

[a]Exposure by inhalation to VC in air at 10,000, and 6000 ppm of breeders; 4 hr/day for 1 week (from 12th to 18th day of pregnancy). Sprague-Dawley rats, M and F, 19 weeks old (breeders). Breeders (groups I and II) and offsprings (groups III and IV). Results after 143 weeks (end of experiment).

Table 23. Experiment BT14.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac	Mammary MT
I 10,000 ppm (breeders)	16.7	66.7	–	–	–	–	–	–	–	–	–	–	–
II 6000 ppm (breeders)	–	–	–	–	–	–	–	–	–	–	–	–	–
III 10,000 ppm (newborn)	100.0	55.5	34.1 (15/44)	–	–	6.8 (3/44)	45.4 (20/44)	–	–	2.3 (1/44)	2.3 (1/44)	–	–
IV 6000 ppm (newborn)	109.3	58.1	40.5 (17/42)	2.4 (1/42)	2.4 (1/42)	2.4 (1/42)	47.6 (20/42)	–	–	4.8 (2/42)	4.8 (2/42)	–	2.4 (1/42)

[a]Exposure by inhalation to VC in air at 10,000 and 6000 ppm, 4 hr/day, 5 days/week, for 5 weeks (from 1 day to 5 weeks of age). Sprague-Dawley rats, M and F, 21 weeks old (breeders) (groups I and II) and newborn (groups III and IV). Results after 124 weeks (end of experiment).

Table 24. Experiment BT7.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %									
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac
I 10,000 ppm	50.0	10.0	29.6 (8/27)	–	–	–	–	3.7 (1/27)	11.1 (3/27)	7.4 (2/27)	–	–
II 6000 ppm	53.3	20.0	11.5 (3/26)	7.7 (2/26)	3.8 (1/26)	3.8 (1/26)	7.7 (2/26)	7.7 (2/26)	3.8 (1/26)	7.7 (2/26)	–	–
III 2500 ppm	26.7	13.3	12.0 (3/25)	–	4.0 (1/25)	–	4.0 (1/25)	–	4.0 (1/25)	–	4.0 (1/25)	–
IV 500 ppm	30.0	10.0	10.7 (3/28)	3.6 (1/28)	–	–	–	7.1 (2/28)	–	–	–	–
V 250 ppm	13.3	16.7	3.7 (1/27)	–	3.7 (1/27)	3.7 (1/27)	–	–	–	–	3.7 (1/27)	–
VI 50 ppm	16.7	6.7	–	–	–	–	–	3.6 (1/28)	–	–	–	–
VII No treatment (control)	15.0	15.0	–	–	2.6 (1/38)	–	–	–	–	–	–	–

[a]Exposure by inhalation to VC in air at 10,000, 6000, 2500, 500, 250, and 50 ppm; 4 hr/day, 5 days/week, for 52 weeks. Wistar rats, M, 13 weeks old. Results after 165 weeks (end of experiment).

Table 25. Experiment BT17.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %									
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac
I 1 ppm	24.2	29.2	–	1.0 (1/99)	3.0 (3/99)	5.0 (5/99)	1.0 (1/99)	–	–	2.0 (2/99)	–	–
II No treatment (control)	20.0	18.5	–	–	–	–	–	–	–	3.2 (3/94)	–	1.1 (1/94)

[a]Exposure by inhalation to VC in air at 1 ppm; 4 hr/day, 5 days/week, for 52 weeks. Wistar rats, M, 13 weeks old. Results after 134 weeks (end of experiment).

Table 26. Experiment BT4.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %							
	MT	BT	LAS	LA	ELAS	ELA	Lung T	Mammary Ca	Skin EpT	Forestomach Pa&Ac
I 10,000 ppm	50.0	98.3	17.8 (10/56)	10.7 (6/56)	1.8 (1/56)	7.1 (4/56)	82.1 (46/56)	23.2 (13/56)	7.1 (4/56)	1.8 (1/56)
II 6000 ppm	56.7	100.0	21.7 (13/60)	11.7 (7/60)	1.7 (1/60)	5.0 (3/60)	78.3 (47/60)	13.3 (8/60)	11.7 (7/60)	1.7 (1/60)
III 2500 ppm	58.3	90.0	27.1 (16/59)	8.5 (5/59)	13.5 (8/59)	1.7 (1/59)	67.8 (40/59)	13.5 (8/59)	6.8 (4/59)	1.7 (1/59)
IV 500 ppm	58.3	108.3	23.3 (14/60)	8.3 (5/60)	11.7 (7/60)	5.0 (3/60)	83.3 (50/60)	13.3 (8/60)	3.3 (2/60)	–
V 250 ppm	63.3	96.3	30.0 (18/60)	18.3 (11/60)	5.0 (3/60)	5.0 (3/60)	68.3 (41/60)	20.0 (12/60)	1.7 (1/60)	1.7 (1/60)
VI 50 ppm	23.3	23.3	1.7 (1/60)	1.7 (1/60)	1.7 (1/60)	8.3 (5/60)	10.0 (6/60)	20.0 (12/60)	–	1.7 (1/60)
VII No treatment (control)	14.7	14.7	–	–	0.7 (1/150)	0.7 (1/150)	10.0 (15/150)	0.7 (1/150)	1.3 (2/150)	–

[a]Exposure by inhalation to VC in air at 10,000, 6000, 2500, 500, 250, and 50 ppm; 4 hr/day, 5 days/week, for 30 weeks. Swiss mice, M and F, 11 weeks old. Results after 81 weeks (end of experiment).

Table 27. Experiment BT8.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELA	Hepatomas	Cholangio-Ca	Cholangiomas	Acoustic Duct EpT	Skin EpT	Melanomas	Forestomach Pa&Ac	Leukaemias[b]
I 10,000 ppm	50.0	73.3	–	3.3 (1/30)	6.7 (2/30)	–	6.7 (2/30)	13.3 (4/30)	3.3 (1/30)	23.3 (7/30)	3.3 (1/30)	33.3 (10/30)	16.7 (5/30)
II 6000 ppm	40.0	63.3	3.3 (1/30)	3.3 (1/30)	–	3.3 (1/30)	6.7 (2/30)	16.7 (5/30)	6.7 (2/30)	3.3 (1/30)	6.7 (2/30)	33.3 (10/30)	20.0 (6/30)
III 2500 ppm	43.3	103.3	–	6.7 (2/30)	–	–	–	26.7 (8/30)	3.3 (1/30)	10.0 (3/30)	3.3 (1/30)	56.7 (17/30)	30.0 (9/30)
IV 500 ppm	53.3	63.3	6.7 (2/30)	–	3.3 (1/30)	–	–	20.0 (6/30)	10.0 (3/30)	23.3 (7/30)	–	30.0 (9/30)	16.7 (5/30)
V 250 ppm	30.0	43.3	–	–	3.3 (1/30)	–	–	20.0 (6/30)	–	10.0 (3/30)	3.3 (1/30)	13.3 (4/30)	20.0 (6/30)
VI 50 ppm	50.0	40.0	–	–	–	–	–	23.3 (7/30)	–	30.0 (9/30)	3.3 (1/30)	10.0 (3/30)	20.0 (6/30)
VII No treatment (control)	20.0	46.7	–	–	–	–	–	36.7 (22/60)	–	5.0 (3/60)	–	5.0 (3/60)	13.3 (8/60)

[a]Exposure by inhalation to VC in air at 10,000, 6000, 2500, 500, 250, and 50 ppm; 4 hr/day, 5 days/week, for 30 weeks. Golden hamsters, M, 11 weeks old. Results after 109 weeks (end of experiment).
[b]Latency time in weeks: Group I, 16.7; Group II, 27.2; Group III, 30.8; Group IV, 19.0; Group V, 22.5; Group VI, 35.3; Group VII, 36.5.

Table 28. Experiment BT11.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac	Mammary MT
I 50.00 mg/kg	38.7	35.0	21.2 (17/80)	3.7 (3/80)	2.5 (2/80)	2.5 (2/80)	–	2.5 (2/80)	–	1.2 (1/80)	1.2 (1/80)	2.5 (2/80)	5.0 (4/80)
II 16.65 mg/kg	30.0	17.5	12.5 (10/80)	–	–	–	–	3.7 (3/80)	–	2.5 (2/80)	–	1.2 (1/80)	7.5 (6/80)
III 3.33 mg/kg	10.0	25.0	–	–	2.5 (2/80)	1.2 (1/80)	–	–	–	–	–	–	3.7 (3/80)
IV Olive oil (control)	13.7	22.5	–	–	–	–	–	–	–	1.2 (1/80)	1.2 (1/80)	–	5.0 (4/80)

[a]Exposure by ingestion (stomach tube) of VC in olive oil at 50.00, 16.65 and 3.33 mg/kg body weight, once daily, 4-5 days/week, for 52 weeks. Sprague-Dawley rats, M and F, 13 weeks old. Results after 136 weeks (end of experiment).

Table 29. Experiment BT27.[a]

Group and concentration	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac	Mammary MT
I 1.0 mg/kg	24.7	35.3	2.0 (3/149)	–	0.7 (1/149)	–	0.7 (1/149)	–	–	3.3 (5/149)	–	2.0 (3/149)	8.0 (12/149)
II 0.3 mg/kg	13.3	28.0	0.7 (1/148)	0.7 (1/148)	–	–	0.7 (1/148)	–	–	–	0.7 (1/148)	1.3 (2/148)	2.7 (4/148)
III 0.03 mg/kg	18.0	31.3	–	–	–	–	–	–	–	–	0.7 (1/150)	0.7 (1/150)	9.3 (14/150)
IV Olive oil (control)	16.0	28.7	–	–	–	–	–	–	–	0.7 (1/150)	–	1.3 (2/150)	4.7 (7 150)

[a]Exposure by ingestion (stomach tube) of VC in olive oil at 1.0, 0.3, 0.03 mg/kg body weight, once daily, 4-5 days/week, for 59 weeks. Sprague-Dawley rats, M and F, 10 weeks old. Results after 136 weeks (end of experiment).

Table 30. Experiment BT12.[a]

Group and dose	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac	Mammary MT
I 4.25 mg × 4	13.8	25.0	–	–	–	–	–	–	–	–	–	1.8 (1/56)	1.8 (1/56)
II 4.25 mg × 3	16.7	28.3	–	–	1.9 (1/53)	–	–	–	–	–	–	1.9 (1/53)	1.9 (1/53)
III 4.25 mg × 2	11.7	18.3	–	–	1.8 (1/56)	–	–	–	–	–	1.8 (1/56)	–	5.3 (3/56)
IV 4.25 mg × 1	20.0	35.0	–	–	–	1.8 (1/55)	–	–	–	1.8 (1/55)	–	3.6 (2/55)	3.6 (2/55)
V Olive oil (control)	8.3	31.7	–	–	–	–	–	–	–	–	–	3.6 (2/55)	–

[a] Exposure by intraperitoneal injection of VC, 4.25 mg in olive oil (1 ml), 4, 3, 2 times, at two month intervals or once only. Sprague-Dawley rats, M and F, 17 weeks old. Results after 144 weeks (end of experiment).

Table 31. Experiment BT13.[a]

Group and dose	Tumors/100 animals		Animals with tumors, %										
	MT	BT	LAS	LA	ELAS	ELA	Hepatomas	Nephro-BL	Neuro-BL	Zymbal Gl.Ca	Skin EpT	Forestomach Pa&Ac	Mammary MT
I 4.25 mg	16.0	17.3	–	–	–	–	–	1.3 (1/75)	–	–	–	–	4.0 (3/75)
II Olive oil (control)	13.3	26.7	–	–	–	1.3 (1/75)	–	–	–	1.3 (1/75)	–	–	1.3 (1/75)

[a] Exposure by subcutaneous injection of VC, 4.25 mg, in olive oil (1 ml), single dose. Sprague-Dawley rats, M and F, 21 weeks old. Results after 145 weeks (end of experiment).

Table 32. Incidence of total MT and BT in Sprague-Dawley rats, in relation to concentration of VC administered by inhalation for 52 weeks.

Experiments	Concentration (ppm)	Tumors/100 animals					
		MT			BT		
		M	F	Total	M	F	Total
BT 6	30,000	76.7	123.3	100.0	40.0	60.0	50.0
BT 1	10,000	80.0	68.3	51.7	26.7	20.0	23.3
	6,000	46.7	73.3	60.0	13.3	63.3	38.3
	2,500	53.3	73.3	63.3	16.7	23.3	20.0
	500	23.3	80.0	51.7	13.3	13.3	13.3
	250	23.3	36.7	30.0	23.3	26.7	25.0
BT 2	200	40.0	30.0	35.0	10.0	33.3	21.7
	150	21.7	48.3	35.0	21.7	28.3	25.0
	100	23.3	20.0	21.7	20.0	35.0	27.5
BT 1	50	6.7	23.3	15.0	23.3	50.0	36.7
BT 9	50	20.7	68.0	44.3	23.3	60.0	41.7
BT 15	25	20.0	46.7	33.3	31.7	85.0	58.3
	10	18.3	45.0	31.7	30.0	76.7	53.3
	5	25.0	46.7	35.8	28.3	81.7	55.0
	1	15.0	30.0	22.5	18.3	70.0	44.2
Controls							
BT 1	0	–	26.7	13.3	23.3	63.3	43.3
BT 2	0	15.3	16.0	15.7	21.2	22.0	21.6
BT 9	0	16.0	30.0	23.0	4.0	44.0	24.0
BT 15	0	18.3	28.3	23.3	20.0	55.0	37.5

Table 33. Incidence of LAS, LA, A+ +/+ + + † and A+ +/+ + + in Sprague-Dawley rats in relation to concentration of VC administered by inhalation for 52 weeks.

Experiments	Concentration, ppm	Animals with tumors and correlated changes, %											
		LAS			LA			A+ +/+ + + †			A+ +/+ + +		
		M	F	Total	M	F	Total	M	F	Total	M	F	Total
BT 6	30,000	16.6	43.3	30.0	–	3.3	1.7	6.7	6.7	6.7	6.7	13.3	10.0
BT 1	10,000	10.0	13.3	11.7	–	–	–	–	3.3	1.7	3.3	6.7	5.0
	6,000	10.3	33.3	22.0	–	6.7	3.4	–	–	–	20.0	16.7	18.3
	2,500	20.0	23.3	21.7	–	–	–	–	–	–	13.3	13.3	13.3
	500	–	20.0	10.0	–	–	–	3.3	–	1.7	13.3	6.7	10.0
	250	3.4	6.7	5.1	–	3.3	1.7	–	–	–	20.0	10.0	15.0
BT 2	200	11.7	8.3	10.0	3.3	3.3	3.3	6.6	5.0	5.8	18.3	10.0	14.1
	150	1.7	8.3	5.0	–	–	–	3.3	10.0	9.2	18.3	6.6	12.5
	100	–	1.7	0.8	1.7	–	0.8	1.7	6.6	4.2	3.3	5.0	6.6
BT 1, BT 9	50	1.1	7.2	4.2	1.1	3.3	2.2	1.7	1.1	1.4	5.5	15.5	10.5
BT 15	25	1.7	6.7	4.2	–	1.7	0.8	1.7	–	0.8	3.3	5.0	4.2
	10	–	1.7	0.8	–	–	–	1.7	–	0.8	1.7	1.7	1.7
	5	–	–	–	–	–	–	–	–	–	–	–	–
	1	–	–	–	–	–	–	–	–	–	–	–	–
Control BT 1, BT 2, BT 9, BT 15	0	–	–	–	–	–	–	–	–	–	–	2.5	1.3

Table 34. Incidence of ELAS, and ELA in Sprague-Dawley rats in relation to concentration of VC administered by inhalation for 52 weeks.

Experiments	Concentration, ppm	Animals with tumors, %					
		ELAS			ELA		
		M	F	Total	M	F	Total
BT 6	30,000	–	3.3	1.7	3.3	6.7	5.0
BT 1	10,000	6.7	3.3	5.0	6.7	3.3	5.0
	6,000	3.4	6.7	5.1	6.9	6.7	6.8
	2,500	6.7	3.3	5.0	3.3	3.3	3.3
	500	–	3.3	1.7	3.3	–	1.7
	250	3.4	3.3	3.4	–	–	–
BT 2	200	1.7	–	0.8	–	1.7	0.8
	150	–	–	–	–	1.7	0.8
	100	–	–	–	–	–	–
BT 1, BT 9	50	2.3	3.3	2.8	4.6	2.8	3.7
BT 15	25	–	–	–	5.0	–	2.5
	10	3.3	–	1.7	3.3	1.7	2.5
	5	–	–	–	–	–	–
	1	–	–	–	–	–	–
Controls BT 1, BT 2, BT 9, BT 15	0	0.9	–	0.4	0.4	0.8	0.6

Table 35. Incidence of hepatomas, neoplastic liver nodules, nodular hyperplasia of the liver and diffuse hyperplasia of the liver in Sprague-Dawley rats in relation to concentration of VC administered by inhalation for 52 weeks.

Experiments	Concentration, ppm	Animals with tumors and correlated changes, %											
		Hepatomas			Neopl. nod.			Nod. hyp.			Diff. hyp.		
		M	F	Total	M	F	Total	M	F	Total	M	F	Total
BT 6	30,000	–	3.3	1.7	3.3	13.3	8.3	13.3	10.0	11.7	–	–	–
BT 1	10,000	3.3	–	1.7	–	–	–	3.3	3.3	3.3	3.3	6.7	5.0
	6,000	–	3.3	1.7	3.3	–	1.7	13.3	6.7	10.0	3.3	3.3	3.3
	2,500	–	6.7	3.3	–	3.3	1.7	6.7	13.3	10.0	–	3.3	1.7
	500	–	16.7	8.3	–	–	–	–	10.0	5.0	13.3	6.7	10.0
	250	3.3	–	1.7	–	–	–	23.3	–	11.7	3.3	–	1.7

Table 35 (cont.)

Experiments	Concentration, ppm	Animals with tumors and correlated changes, %											
		Hepatomas			Neopl. nod.			Nod. hyp.			Diff. hyp.		
		M	F	Total	M	F	Total	M	F	Total	M	F	Total
BT 2	200	1.7	3.3	2.5	3.3	1.7	2.5	20.0	13.3	16.7	33.3	18.3	26.3
	150	–	–	–	1.7	–	0.8	3.3	13.3	10.8	16.7	25.3	20.8
	100	–	–	–	–	–	–	5.0	23.3	14.2	26.7	13.3	20.0
BT 1, BT 9	50	–	–	–	0.5	–	0.3	13.3	9.4	11.4	2.8	3.3	3.0
BT 15	25	–	–	–	–	–	–	15.0	8.3	11.7	5.0	10.0	7.5
	10	–	–	–	–	–	–	20.0	5.0	12.5	10.0	6.7	8.3
	5	–	–	–	–	–	–	1.7	–	0.8	–	–	–
	1	–	–	–	–	–	–	3.3	–	1.7	1.7	–	0.8
Controls BT 1, BT 2, BT 9, BT 15	0	–	–	–	–	0.4	0.2	0.4	0.8	0.6	0.9	2.9	1.9

Table 36. Incidence of nephroblastoma in Sprague-Dawley rats in relation to concentration of VC administered by inhalation for 52 weeks.

Experiment	Concentration, ppm	Animals with NEPHRO-BL, %		
		M	F	Total
BT 6	30,000	–	–	–
BT 1	10,000	10.0	6.7	8.3
	6,000	13.3	3.3	8.5
	2,500	16.7	3.3	10.0
	500	6.7	13.3	10.0
	250	3.4	13.3	8.5
BT 2	200	3.3	3.3	5.8
	150	13.3	5.0	9.2
	100	13.3	3.3	8.3
BT 1, BT 9	50	–	1.1	0.6
BT 15	25	1.7	–	0.8
	10	–	–	–
	5	–	–	–
	1	–	–	–
Controls BT 1, BT 2, BT 9, BT 15	0	–	–	–

Table 37. Incidence of neuroblastoma in Sprague-Dawley rats in relation to concentration of VC administered by inhalation for 52 weeks.

Experiments	Concentration, ppm	Animals with NEURO-BL, %		
		M	F	Total
BT 6	30,000	3.3	–	1.7
BT 1	10,000	6.7	16.7	11.7
	6,000	6.9	3.3	5.1
	2,500	6.7	6.7	6.7
	500	–	–	–
	250	–	–	–
BT 2	200	–	–	–
	150	–	–	–
	100	–	–	–
BT 1, BT 9	50	–	–	–
BT 15	25	–	–	–
	10	–	–	–
	5	–	–	–
	1	–	–	–
Controls BT 1, BT 2, BT 9, BT 15	0	–	–	–

Table 38. Incidence of zymbal gland carcinoma in Sprague-Dawley rats in relation to concentration of VC administered by inhalation for 52 weeks.

Experiment	Concentration, ppm	Animals with Zymbal gland CA, %		
		M	F	Total
BT 6	30,000	56.6	60.0	58.3
BT 1	10,000	33.3	20.0	26.7
	6,000	10.3	13.3	11.9
	2,500	3.3	3.3	3.3
	500	10.0	3.3	6.7
	250	–	–	–
BT 2	200	5.0	1.7	3.3
	150	–	6.7	3.4
	100	–	1.7	0.8
BT 1, BT 9	50	2.3	2.8	2.5
BT 15	25	5.0	1.7	3.3
	10	1.7	1.7	1.7
	5	–	1.7	0.8
	1	1.7	–	0.8
Controls BT 1, BT 2, BT 9, BT 15	0	0.9	0.8	0.9

Table 39. Incidence of forestomach papilloma and acanthoma in Sprague-Dawley rats in relation to concentration of VC administered by inhalation for 52 weeks.

Experiment	Concentration, ppm	Animals with forestomach Pa and Ac, %		
		M	F	Total
BT 6	30,000	16.7	20.0	18.3
BT 1	10,000	–	–	–
	6,000	–	3.3	1.7
	2,500	–	–	–
	500	–	–	–
	250	–	–	–
BT 2	200	–	–	–
	150	3.3	–	1.7
	100	3.3	3.3	3.3
BT 1, BT 9	50	1.1	–	0.6
BT 15	25	–	–	–
	10	–	–	–
	5	–	–	–
	1	–	–	–
Controls BT 1, BT 2, BT 9, BT 15	0	1.3	0.4	0.9

their onset, even at doses below the ones with statistically significant results.

An excess of Zymbal gland carcinomas is observed down to 50 and 25 ppm.

Liver angiosarcomas are extremely rare in the colony used (4 cases over several thousand untreated animals). Therefore, one must consider the onset of these tumors as important even at doses not shown by statistical analysis, and particularly below 50 ppm (5 liver angiosarcomas out of 120 animals at 25 ppm, and 1 liver angiosarcoma out of 120 animals at 10 ppm), and at 1 mg/kg (3 liver angiosarcomas out of 150 animals), and at 0.3 mg/kg (1 liver angiosarcoma out of 150 animals).

The onset of a few nephroblastomas observed after inhalation treatment at doses below 100 ppm and in groups treated by ingestion with 50 and 16.65 mg/kg, is not casual in our opinion, given the extreme rarity of these tumors in rats.

Neuroblastomas have never been observed by us, up to the present, in the Sprague-Dawley rats used in our laboratory as control or otherwise

Table 40. Incidence of mammary malignant tumor in female Sprague-Dawley rats in relation to concentration of VC administered by inhalation for 52 weeks.

Experiment	Concentration, ppm	Animals with Mammary MT, %
BT 6	30,000	6.7
BT 1	10,000	10.0
	6,000	–
	2,500	6.7
	500	3.3
	250	6.7
BT 2	200	8.3
	150	10.0
	100	6.7
BT 1	50	6.7
BT 9	50	40.7
BT 15	25	28.3
	10	35.0
	5	38.3
	1	28.3
Controls		
BT 1	0	–
BT 2	0	2.0
BT 9	0	18.0
BT 17	0	10.0

Table 41. Incidence of total MT and BT in male Wistar rats in relation to concentration of VC administered by inhalation for 52 weeks.

Experiment	Concentration, ppm	Tumors/100 Animals	
		MT	BT
BT 7	10,000	50.0	10.0
	6,000	53.3	20.0
	2,500	26.7	13.3
	500	30.0	10.0
	250	13.3	16.7
	50	16.7	6.7
BT 17	1	24.2	29.2
Controls			
BT 7	0	15.0	15.0
BT 17	0	20.0	18.5

Table 43. Incidence of ELAS and ELA in male Wistar rats in relation to concentration of VC administered by inhalation for 52 weeks.

Experiment	Concentration, ppm	Animals with tumors, %	
		ELAS	ELA
BT 7	10,000	–	–
	6,000	3.8	3.8
	2,500	4.0	–
	500	–	–
	250	3.7	3.7
	50	–	–
BT 17	1	3.0	5.0.
Controls BT 7, BT 17	0	0.7	–

treated. Therefore we consider as dependent on treatment the onset of these tumors, even at doses below 10,000 ppm, i.e., 6000 and 2500 ppm.

The meaning in oncological terms of the results at the lowest doses may be better evaluated in considering, not singly, but together, the tumors found to be VC-dependent (Table 71).

None (or no increase) of the specifically VC related tumors shown in Table 71, observed in the seven basic experiments, was found at doses of 5 and 1 ppm (by inhalation) and 0.03 mg/kg (by ingestion).

General Comments

VC long-term experimental study led to the discovery of VC carcinogenicity, and as a direct consequence, to what probably has been the greatest effort ever made at controlling the exposure to an industrial carcinogen in the workplace (Table 72).

Moreover, long-term carcinogenicity bioassays on VC are a crucial step in the field of environmental and occupational carcinogenesis which, in turn,

Table 42. Incidence of LAS, LA, A+ +/+ + + ↑ and A+ +/+ + + in male Wistar rats in relation to concentration of VC administered by inhalation for 52 weeks.

Experiment	Concentration, ppm	Animals with tumors and correlated changes, %			
		LAS	LA	A+ +/+ + + ↑	A+ +/+ + +
BT 7	10,000	29.6	–	3.3	–
	6,000	11.5	7.7	–	3.3
	2,500	12.0	–	3.3	–
	500	10.7	3.6	3.3	3.3
	250	3.7	–	3.3	–
	50	–	–	–	–
BT 17	1	–	1.0	1.7	0.8
Controls BT 7, BT 17	0	–	–	–	–

Table 44. Incidence of hepatomas, neoplastic liver nodules, nodular hyperplasia of the liver and diffuse hyperplasia of the liver in male Wistar rats in relation to concentration of VC administered by inhalation for 52 weeks.

Experiment	Concentration, ppm	Animals with tumors and correlated changes, %			
		Hepatomas	Neop.nod.	Nod.hyp.	Dif.hyp.
BT 7	10,000	–	–	6.7	–
	6,000	7.7	6.7	3.3	6.7
	2,500	4.0	–	6.7	6.7
	500	–	6.7	–	3.3
	250	–	–	–	16.7
	50	–	–	–	10.0
BT 17	1	1.0	–	5.0	4.2
Controls BT 7, BT 17	0	–	–	1.2	2.3

Table 45. Incidence of NEPHRO-BL in male Wistar rats in relation to concentration of VC administered by inhalation for 52 weeks.

Experiment	Concentration, ppm	Animals with NEPHRO-BL, %
BT 7	10,000	3.7
	6,000	7.7
	2,500	–
	500	7.1
	250	–
	50	3.6
BT 17	1	–
Controls BT 7, BT 17	0	–

Table 46. Incidence of NEURO-BL in male Wistar rats in relation to concentration of VC administered by inhalation for 52 weeks.

Experiment	Concentration, ppm	Animals with NEURO-BL, %
BT 7	10,000	11.1
	6,000	3.8
	2,500	4.0
	500	–
	250	–
	50	–
BT 17	1	–
Controls BT 7, BT 17	0	–

Table 47. Incidence of Zymbal gland CA in male Wistar rats in relation to concentration of VC administered by inhalation for 52 weeks.

Experiment	Concentration, ppm	Animals with Zymbal gland CA, %
BT 7	10,000	7.4
	6,000	7.7
	2,500	–
	500	–
	250	–
	50	–
BT 17	1	2.0
Controls BT 7, BT 17	0	2.3

Table 48. Incidence of forestomach Pa and Ac in male Wistar rats in relation to concentration of VC administered by inhalation for 52 weeks.

Experiment	Concentration, ppm	Animals with forestomach Pa and Ac, %
BT 7	10,000	–
	6,000	–
	2,500	–
	500	–
	250	–
	50	–
BT 17	1	–
Controls BT 7, BT 17	0	0.7

are among the most important areas of public health nowadays.

These studies have demonstrated that long-term carcinogenicity bioassays: may predict carcinogenic risk for humans; may give indication of the level of risk, in relation to dose; may provide information on possible target organs and, in general terms, on the quality of neoplastic response; may represent a tool for obtaining information on the relative risk represented by different compounds, provided that they are tested under the same standard conditions (Table 73); have revealed the need to identify

Table 49. Incidence of total MT and BT in Swiss mice in relation to concentration of VC administered by inhalation for 30 weeks.

Experiment	Concentration, ppm	Tumors/100 animals					
		MT			BT		
		M	F	Total	M	F	Total
BT 4	10,000	16.6	83.3	50.0	83.3	113.3	98.3
	6,000	26.7	86.6	56.7	100.0	100.0	100.0
	2,500	40.0	76.7	58.3	80.0	100.0	90.0
	500	36.7	80.0	58.3	96.3	113.3	103.3
	250	36.7	90.0	63.3	116.7	80.0	98.3
	50	6.7	50.0	28.3	20.0	26.7	23.3
	0	6.2	24.3	14.7	13.7	15.7	14.7

Table 50. Incidence of LAS and LA in Swiss mice in relation to concentration of VC administered by inhalation for 30 weeks.

Experiment	Concentration, ppm	Animals with tumors, %					
		LAS			LA		
		M	F	Total	M	F	Total
BT 4	10,000	3.3	30.0	17.8	3.3	16.7	10.7
	6,000	6.7	36.7	21.7	6.7	16.7	11.7
	2,500	20.7	33.3	27.1	6.9	10.0	8.5
	500	20.0	26.7	23.3	3.3	13.3	8.3
	250	30.0	30.0	30.0	20.0	16.7	18.3
	50	3.3	-	1.7	-	3.3	1.7
	0	-	-	-	-	-	-

Table 51. Incidence of ELAS and ELA in Swiss mice in relation to concentration of VC administered by inhalation for 30 weeks.

Experiment	Concentration, ppm	Animals with tumors, %					
		ELAS			ELA		
		M	F	Total	M	F	Total
BT 4	10,000	-	3.3	1.8	7.7	6.7	7.1
	6,000	-	3.3	1.7	6.7	3.3	5.0
	2,500	13.8	13.3	13.5	-	3.3	1.7
	500	6.7	16.7	11.7	3.3	6.7	5.0
	250	6.7	3.3	5.0	6.7	3.3	5.0
	50	3.3	-	1.7	3.3	13.3	8.3
	0	-	1.4	0.7	1.2	-	0.7

Table 52. Incidence of lung tumors (Ad and Ad †) in Swiss mice in relation to concentration of VC administered by inhalation for 30 weeks.

Experiment	Concentration, ppm	Animals with lung tumors (Ad and Ad †), %		
		M	F	Total
BT 4	10,000	76.9	86.7	82.1
	6,000	76.7	80.0	78.3
	2,500	62.1	73.3	67.8
	500	80.0	86.7	83.3
	250	80.0	56.7	68.3
	50	10.0	10.0	10.0
	0	10.0	10.0	10.0

Table 53. Incidence of mammary CA in female Swiss mice in relation to concentration of VC administered by inhalation for 30 weeks.

Experiment	Concentration, ppm	Animals with mammary CA, %
BT 4	10,000	43.3
	6,000	26.7
	2,500	26.7
	500	23.3
	250	40.0
	50	40.0
	0	1.4

animal systems more equivalent to humans in neoplastic response, which in turn depends on partly-known factors, such as basic "spontaneous" tumorigram and enzymatic profiles.

Prospects

At present the most important goal of research on environmental and occupational carcinogenesis is, in our own view, the extrapolation of results

Table 54. Incidence of forestomach Pa and Ca in Swiss mice in relation to concentration of VC administered by inhalation for 30 weeks.

Experiment	Concentration, ppm	Animals with forestomach Pa and Ac, %		
		M	F	Total
BT 4	10,000	–	3.3	1.8
	6,000	3.3	–	1.7
	2,500	–	3.3	1.7
	500	–	–	–
	250	3.3	–	1.7
	50	3.3	–	1.7
	0	–	–	–

Table 55. Incidence of total MT and BT in Sprague-Dawley rats in relation to concentration of VC administered by ingestion for 52 (or 59) weeks.

Experiment	Concentration, mg/kg	Tumors/100 animals					
		MT			BT		
		M	F	Total	M	F	Total
BT 11	50.00	35.0	42.5	38.7	20.0	50.0	35.0
	16.65	22.5	37.5	30.0	–	35.0	17.5
	3.33	5.0	15.0	10.0	2.5	47.5	25.0
BT 27	1.0	13.3	36.0	24.7	12.0	58.7	35.3
	0.3	12.0	14.7	13.3	20.0	36.0	28.0
	0.03	8.0	28.0	18.0	14.7	48.0	31.3
Controls							
BT 11	0	12.5	15.0	13.7	10.0	35.0	22.5
BT 27	0	8.0	24.0	16.0	9.3	48.0	28.7

Table 56. Incidence of LAS, LA, A+ +/+ + + ↑ and A+ +/+ + + in Sprague-Dawley rats in relation to concentration of VC administered by ingestion for 52 (or 59) weeks.

Experiment	Concentration, mg/kg	Animals with tumors and correlated changes, %											
		LAS			LA			A+ +/+ + + ↑			A+ +/+ + +		
		M	F	Total	M	F	Total	M	F	Total	M	F	Total
BT 11	50.00	20.0	22.5	21.2	2.5	5.0	3.7	7.5	5.0	12.5	7.5	10.0	8.7
	16.65	10.0	15.0	12.5	–	–	–	5.0	5.0	5.0	7.5	15.0	11.2
	3.33	–	–	–	–	–	–	2.5	7.5	5.0	15.0	22.5	18.7
BT 27	1.0	1.3	2.7	2.0	–	–	–	–	–	–	1.3	6.7	4.0
	0.3	–	1.4	0.7	–	1.4	0.7	–	1.3	0.7	1.3	1.3	1.3
	0.03	–	–	–	–	–	–	–	–	–	–	–	–
Controls BT 11, BT 27	0	–	–	–	–	–	–	–	0.9	0.4	–	0.9	0.4

Table 57. Incidence of ELAS and ELA in Sprague-Dawley rats in relation to concentration of VC administered by ingestion for 52 (or 59) weeks.

Experiments	Concentration, mg/kg	Animals with tumors, %					
		ELAS			ELA		
		M	F	Total	M	F	Total
BT 11	50.00	–	5.0	2.5	2.5	2.5	2.5
	16.65	–	–	–	–	–	–
	3.33	–	5.0	2.5	–	2.5	1.2
BT 27	1.0	–	1.3	0.7	–	–	–
	0.3	–	–	–	–	–	–
	0.03	–	–	–	–	–	–
Controls BT 11, BT 27	0	–	–	–	–	–	–

Table 58. Incidence of hepatomas, neoplastic liver nodules, nodular hyperplasia of the liver, and diffuse hyperplasia of the liver in Sprague-Dawley rats in relation to concentration of VC administered by ingestion for 52 (or 59) weeks.

Experiments	Concentration, mg/kg	Animals with tumors and correlated changes, %											
		Hepatomas			Neop.nod.			Nod.hyp.			Dif.hyp.		
		M	F	Total	M	F	Total	M	F	Total	M	F	Total
BT 11	50.00	–	–	–	–	5.0	2.5	17.5	17.5	17.5	15.0	15.0	15.0
	16.65	–	–	–	–	–	–	17.5	30.0	23.7	25.0	32.5	28.7
	3.33	–	–	–	2.5	–	1.2	10.0	20.0	15.0	15.0	42.5	28.7
BT 27	1.0	1.3	–	0.7	1.3	2.7	2.0	6.7	13.3	10.0	6.7	14.7	10.7
	0.3	1.3	–	0.7	–	1.3	0.7	9.3	6.7	8.0	–	10.7	5.3
	0.03	–	–	–	–	–	–	4.0	6.7	5.3	–	10.7	5.3
Controls BT 11, BT 27	0	–	–	–	–	0.9	0.4	5.2	6.1	5.6	7.0	8.7	7.8

Table 59. Incidence of NEPHRO-BL in Sprague-Dawley rats in relation to concentration of VC administered by ingestion for 52 (or 59) weeks.

Experiments	Concentration, mg/kg	Animals with NEPHRO-BL, %		
		M	F	Total
BT 11	50.00	2.5	2.5	2.5
	16.65	5.0	2.5	3.7
	3.33	–	–	–
BT 27	1.0	–	–	–
	0.3	–	–	–
	0.03	–	–	–
Controls BT 11, BT 27	0	–	–	–

Table 60. Incidence of NEURO-BL in Sprague-Dawley rats in relation to concentration of VC administered by ingestion for 52 (or 59) weeks.

Experiments	Concentration, mg/kg	Animals with NEURO-BL, %		
		M	F	Total
BT 11	50.00	–	–	–
	16.65	–	–	–
	3.33	–	–	–
BT 27	1.0	–	–	–
	0.3	–	–	–
	0.03	–	–	–
Controls BT 11, BT 27	0	–	–	–

from animal to human, both in qualitative and in quantitative terms.

VC carcinogenicity may again provide an important tool towards solving this problem.

We now know a great deal about the effects of VC in experimental animal systems, both in qualitative and quantitative terms.

On the other hand, epidemiological investigations on occupationally exposed population groups have been made and are being carried out in different parts of the world, particularly in Western Europe and in the U.S.A., with reference to general pathology and neoplasias.

If these epidemiological investigations provide precise figures on the whole group considered, including figures on the level and length of expo-

Table 61. Incidence of Zymbal gland CA in Sprague-Dawley rats in relation to concentration of VC administered by ingestion for 52 (or 59) weeks.

Experiments	Concentration, mg/kg	Animals with Zymbal gland CA, % M	F	Total
BT 11	50.00	2.5	–	1.2
	16.65	2.5	2.5	2.5
	3.33	–	–	–
BT 27	1.0	2.7	4.0	3.3
	0.3	–	–	–
	0.03	–	–	–
Controls BT 11, BT 27	0	–	1.7	0.9

Table 62. Incidence of forestomach Pa and Ac in Sprague-Dawley rats in relation to concentration of VC administered by ingestion for 52 (or 59) weeks.

Experiments	Concentration, mg/kg	Animals with forestomach Pa and Ac, % M	F	Total
BT 11	50.00	5.0	–	2.5
	16.65	–	2.5	1.2
	3.33	–	–	–
BT 27	1.0	1.3	2.7	2.0
	0.3	2.7	–	1.3
	0.03	–	1.3	0.7
Controls BT 11, BT 27	0	–	1.7	0.9

Table 63. Incidence of mammary MT in female Sprague-Dawley rats in relation to concentration of VC administered by ingestion for 52 (or 59) weeks.

Experiment	Concentration mg/kg	Animals with mammary MT, %
BT 11	50.00	10.0
	16.65	15.0
	3.33	5.0
BT 27	1.0	16.0
	0.3	5.5
	0.03	18.7
Controls		
BT 11	0	10.0
BT 27	0	9.3

sure (so as to define homogeneous exposed groups), and collect all possible available data on pathology, we shall have an opportunity, unique at present, to compare animal and human data, both in qualitative and quantitative terms, and to help find a possible key for extrapolating from animals to humans.

The Cost

With the presentation made in Paris last November (2) and with today's report, ten years of work on our VC experimental project seem to be nearly concluded. After having presented the results, we also wish to present the data of the cost of the project, which cannot be expressed only in financial terms.

The cost of the BT project of long-term carcinogenicity bioassays on vinyl chloride includes the cost of (1) the planning and setting-up of experimental apparatus, including inhalation facilities, of

Table 64. Incidence of LAS and Zymbal gland CA in Sprague-Dawley rats in relation to schedule of treatment with VC administered by inhalation.

Experiment	VC concentration, ppm	Schedule[a]	Animals with tumors, % LAS M	LAS F	LAS Total	Zymbal gl.ca M	Zymbal gl.ca F	Zymbal gl.ca Total
BT 1	10,000	I	10.0	13.3	11.7	33.3	20.0	26.7
BT 3	10,000	II	–	–	–	17.6	13.3	15.5
BT 10	10,000	III	1.7	–	0.8	13.5	1.7	7.6
		IV	1.7	–	0.8	8.5	6.7	7.6
		V	–	1.7	0.8	3.3	10.2	6.7
BT 1	6,000	I	10.3	33.3	22.0	10.3	13.3	11.9
BT 3	6,000	II	–	3.3	1.7	20.0	10.0	15.0
BT 10	6,000	III	–	–	–	10.0	5.0	7.5
		IV	3.4	1.7	2.5	8.5	–	4.2
		V	–	1.7	0.8	10.0	5.0	7.5

[a]Schedules: (I) 4 hr/day, 5 days/wk, 52 weeks; (II) 4 hr/day, 5 days/wk, 17 weeks; (III) 4 hr/day, 5 days/wk, 5 weeks; (IV) 1 hr/day, 4 days/wk, 25 weeks; (V) 4 hr/day, 1 day/wk; 25 weeks.

Table 65. Incidence of LAS in relation to species (male Sprague-Dawley Rats, Wistar rats, Swiss mice and golden hamsters), treated with VC administered by inhalation.

Experiments	Concentration, ppm	Animals with LAS, %			
		Sprague-Dawley rats	Wistar rats	Swiss mice	Golden hamsters
BT1, BT2, BT3, BT5	10,000	10.0	29.6	3.8	–
	6,000	10.3	11.5	6.7	3.3
	2,500	20.0	12.0	20.7	–
	500	–	10.0	20.0	6.7
	250	3.4	3.7	30.0	–
	50	–	–	3.3	–
	0	–	–	–	–

Table 66. Incidence of Zymbal gland CA in relation to strain (male Sprague-Dawley and Wistar rats) treated with VC administered by inhalation.

Experiments	Concentration, ppm	Animals with Zymbal gland CA, %	
		Sprague-Dawley rats	Wistar rats
BT1, BT2	10,000	33.3	7.4
	6,000	10.3	7.7
	2,500	3.3	–
	500	10.0	–
	250	–	–
	50	–	–
	0	–	–

a type uncommon in 1971, and the working out of a protocol for long-term bioassays; (2) the study of nearly 7000 animals up to the point of their natural death, equivalent to more than 3,000,000 rodent days; (3) ten years of work; (4) the routine examination of some 200,000 histological slides; (5) a financial commitment equivalent to more than $2,000,000 U.S. at present prices (the average cost of a rat throughout the world in this type of experiment is $300 U.S.); (6) the availability of the same team of scientists throughout the entire 10 years of the project, a prerequisite which may be difficult or even impossible to ensure in many countries at the present time; (7) the highly motivated commitment of those scientists to a type of work which is long-lasting, onerous and often tedious; (8) the effort involved in maintaining the

Table 67. Incidence of LAS in relation to age (newborn and adult) Sprague-Dawley rats treated with VC administered by inhalation 4 hr/day, 5 days/week, 52 weeks.

Experiment	Concentration, ppm	Animals with LAS, %					
		Newborn rats			11 week old rats		
		M	F	Total	M	F	Total
BT1 to BT14	10,000	25.0	45.0	34.1	1.7	–	0.8
	6,000	27.8	50.0	40.5	–	–	–

Table 68. Tumors presently correlated to VC exposure, by experiments on rodents.

Species	Angiosarcomas of liver	Tumors of brain	Tumors of lung	Lymphomas and leukemias	Hepatomas	Angiosarcomas and angiomas of other sites	Nephroblastomas	Sebaceous cutaneous carcinomas	Other cutaneous epithelial tumors	Mammary carcinomas	Forestomach papillomas and acanthomas	Melanomas
Rat	–	+			+	+	+	+	(+)	+	+	
Mouse	–		+			+			(+)	+	(+)	
Hamster	–			(+)		(+)			(+)		+	(+)

Table 69. Total cancer-bearing animals significantly in excess by Fisher exact probability test ($p \leq 0.05$).

Sex	Dose level at which total cancer bearing animals in excess
Male	30,000
	10,000
	6,000
	2,500
	500
	250
	200
	50 ppm
	50 mg/kg
Female	30,000
	10,000
	6,000
	2,500
	500
	200
	150
	50 ppm
	50 mg/kg

Table 70. Tumors significantly in excess by Fisher exact probability test ($p \leq 0.05$).

Tumor type	Sex	Doses at which tumors in excess
Zymbal gland carcinoma	M	30,000; 10,000 ppm
	F	30,000; 10,000 ppm
Liver angiosarcoma	M	30,000; 2500; 200 ppm 50 mg/kg
	F	30,000; 6000; 2500; 500 200; 150; 50 ppm 50; 16.65 mg/kg
Nephroblastoma	M	2500; 200; 150; 100 ppm
	F	500; 250 ppm
Neuroblastoma	F	10,000 ppm
Mammary gland adenocarcinoma	F	150; 50; 25; 10; 5 ppm
Forestomach papilloma	M	30,000 ppm
	F	30,000 ppm

Table 71. Onset of tumors considered VC-correlated at the lowest doses.

Dose	Tumors
25 ppm	Over 120 animals, 5 liver angiosarcomas, 4 Zymbal gland carcinomas and 1 nephroblastoma
10 ppm	Over 120 animals, 1 liver angiosarcoma, 2 extrahepatic angiosarcomas, and 2 Zymbal gland carcinomas
1 mg/kg	Over 150 animals, 3 liver angiosarcomas, 1 extrahepatic angiosarcoma, 1 hepatoma, and 5 Zymbal gland carcinomas
0.3 mg/kg	Over 150 animals, 1 liver angiosarcoma and 1 hepatoma

Table 72. History of vinyl chloride carcinogenicity studies.

Date	
1961	VC was found to produce liver enlargement and microscopic hepatic degenerative changes (*5*)
1970	Zymbal gland carcinomas were reported in rats exposed to 30,000 ppm of VC, by inhalation (*6*)
1970	An increase in atypias in respiratory cells was observed among workers heavily exposed to VC (*7*)
July 1971	A vast project of long-term carcinogenicity bioassays on VC was started in Bentivoglio, near Bologna, Italy (BT project)
August 1972	Zymbal gland carcinomas, nephroblastomas and liver angiosarcomas were observed in rats exposed to VC by inhalation (Maltoni, BT project)
April 1973	The first data of the BT project were released to the scientific community: the oncogenic effect was observed up to 250 ppm (*4*)
1973	Splenomegalic liver disease was found among poly(vinyl chloride) production workers (*8*)
December 1973	For the first time a case of liver angiosarcoma in a poly(vinyl chloride) production worker was correlated to VC exposure (*9*)
February 1974	On the basis of the BT project data indicating a carcinogenic effect at 250 ppm, OSHA proposed a TLV of 50 ppm
February 1974	The BT project data showed that VC is a multipotential carcinogen, producing a variety of tumors, in different animal species
1974	The BT project data indicated a carcinogenic effect at 50 ppm (*10*); OSHA proposed new stricter rules
1974	Early epidemiological observations (paralleling the experimental information) indicated an increase in tumors other than liver angiosarcomas (of brain, lung, liver, hemolymphoreticular tissues) among workers of VC-PVC industries (*11*)
1974–75	BT project data showed that VC had carcinogenic effects in rats also when given by ingestion (*12*)
1976	In rats of the BT project exposed to VC by inhalation, angiosarcomas were observed down to the level of 25 ppm, and Zymbal gland carcinomas down to the level of 10 ppm (*13*)

consistency of the methodology, which has as its reverse side the limits placed on the exercise of imagination—the most positive element in scientific life; (9) the effort involved in establishing and preserving objectivity and balance in the evaluation and interpretation of data; (10) and finally, the strength required to withstand the sense of loneliness arising from the lack of co-operation of many of those bodies which should properly be concerned with the progress of science in this field, not excluding part of the scientific community whose

Table 73. Comparative effects of three related compounds—vinyl chloride (VC), vinylidene chloride (VDC) and ethylene dichloride (EDC) on the same animal systems.

Compound	Species	Angiosarcomas of liver	Tumors of the brain	Tumors of the lung	Hepatomas	Angiosarcomas and angiomas of other sites	Tumors of the kidney: Nephroblastomas	Tumors of the kidney: Adenocarcinomas	Sebaceous cutaneous carcinomas	Other cutaneous epithelial tumors	Mammary carcinomas	Forestomach papillomas and acanthomas
VC	Rat (Sprague-Dawley)	+	+		+	+	+		+	(+)	+	+
	Mouse (Swiss)	+		+		+				(+)	+	(+)
VDC	Rat (Sprague-Dawley)											
	Mouse (Swiss)			(+)				+				
EDC	Rat (Sprague-Dawley)											
	Mouse (Swiss)		[illegible]									

indifference sometimes degenerates into frank hostility.

The high costs probably represent the reason why, in the field of experimental and environmental carcinogenesis, words overlap facts, opinions overlap data, and meetings and commissions reports submerge good laboratory work.

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Neoplastic and Nonneoplastic Effects of Vinyl Chloride in Mouse Lung

by Yasunosuke Suzuki*

Neoplastic effects of vinyl chloride were studied in lungs of 27 mice exposed to vinyl chloride monomer at 2500 and 6000 ppm for 5 and 6 months (large doses and long-term exposure). Pulmonary tumors were observed in 26 of 27 experimental animals. Light microscopy showed the tumors to be multiple and arranged in either tubulo-papillary or adenomatous formations. Although occasional mitotic divisions and invaginations into the bronchiolar lumen were observed, no metastases were found. By electron microscopy, short microvilli, tight junctions between two adjacent cells, appearance of osmiophilic lamellar bodies, large mitochondria of irregular shape, well developed Golgi complexes, continuous or discontinuous basement membranes, occasional appearance of "sequestration" and of crystalloids and lack of both cilia and mucous secretory granules were observed as characteristic features of the neoplastic cells. Some of the cells were poorly differentiated and were equipped with poorly developed organoids, without formation of osmiophilic lamellar bodies. The pulmonary tumors corresponded to "alveologenic" tumors. It is suggested that the neoplastic cells were transformed from type II alveolar epithelium via its hyperplastic form.

Nonneoplastic effects of the chemical were also studied in the 27 mice. Major light microscopic alterations observed were proliferation and hypertrophy of the terminal bronchiolar cells, consisting of ciliated and Clara cells, hypersecretion of the epithelial mucin in the goblet cells of both the bronchial and the proximal bronchiolar epithelium, hyperplasia of alveolar epithelium, mobilization of alveolar macrophages and occasional presence of peribronchial or bronchiolar chronic inflammation. Electron microscopically, Clara cells of the terminal bronchiolar epithelium showed proliferation of the rough and smooth surfaced endoplasmic reticulum and appearance of large and abnormally shaped mitochondria. Similar alterations were found in the ciliated cells. Submicroscopic changes of pulmonary alveoli were represented by focal thickening of the basement membrane, multiple foci of hyperplastic type II cell (the precondition of the alveologenic tumor), active discharge of osmiophilic lamellar bodies from the type II cell and phagocytosis of the bodies by macrophages, appearance of cholesterol crystalloids in the macrophages, degeneration of alveolar septal cells and occasional appearance of a large nucleus with swelling of the capillary endothelium.

The neoplastic effect of vinyl chloride of smaller doses (100, 10, 1 and 0 [control] ppm) and shorter exposure (four weeks) was studied in lungs of 120 mice. Our preliminary observation indicated that sacrificed animals at 40 weeks after the exposure showed productions of the alveologenic tumor in 5 of 9 (100 ppm), 2 of 9 (10 ppm), 1 of 9 (1 ppm) and 0 of 10 (control = 0 ppm). A dose-response relation was considered in the incidence of the alveologenic tumor production of vinyl chloride. It is concluded that mouse lung is an extremely sensitive indicator of the oncogenicity of vinyl chloride.

Introduction

Hepatic hemangiosarcoma has been accepted as a serious health hazard associated with vinyl chloride exposure among workers in vinyl chloride polymerization plants (*1-7*). A risk of lung cancer has also been reported among the workers on the basis of epidemiological studies (*8,9*).

Experimental studies in rats, mice, and hamsters have shown that, in addition to liver, various organs such as lung, brain, breast and skin, including sebaceous glands, were involved in induction of primary neoplasia by vinyl chloride. Although a

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number of studies have demonstrated that pulmonary tumors can be induced by vinyl chloride in mice, the significance of such occurrence and the nature of the tumors have not yet been appropriately explored (*10-17*).

The occurrence of the nonneoplastic pulmonary abnormalities among vinyl chloride polymerization workers has been reported on the basis of chest x-ray (*18*), pulmonary function (*19*) and smear cytology (*1*) of the worker's sputum. No histopathological evaluation of the abnormalities has been reported.

It is believed that a relationship between lung cancer and vinyl chloride exposure exists from epidemiological studies (*6,8,9,20*). A high incidence of pulmonary tumors in mice exposed to vinyl chloride has been reported by several investigators (*10-15*). However, the nonneoplastic pulmonary effects of the chemical have not been completely explored. We have, therefore, undertaken detailed light and electron microscopy of the mouse lung, to characterize the neoplastic and nonneoplastic pulmonary effects of vinyl chloride.

FIGURE 1. Two pulmonary tumors induced by vinyl chloride are seen in the peripheral part of a mouse lung (2500 ppm in group III). Hematoxylin and eosin; 64×.

Materials and Methods

Twenty-seven CDI Charles River white strain male mice, 4 to 5 weeks old at first exposure, were used. All of 27 mice used for this study were alive until they were sacrificed at three separate stages. The mice that died in the course of the experiment were excluded from the study. Group I consisted of six animals exposed to vinyl chloride at 2500 (three mice) and 6000 (three mice) ppm/hr, 5 hr/day, 5 days/week, for 5 months. They were then kept for 6 days without exposure before sacrifice. Group II included 13 mice exposed at 2500 (seven mice) and 6000 (six mice) ppm for 6 months and were kept for an additional 2 days for recovering before sacrifice. Group III included eight animals (seven at 2500 ppm and one at 6000 ppm) which were exposed to vinyl chloride monomer for 6 months followed by a 37-day recovery period. The inhalation exposures were accomplished at the Industrial Bio-Test Laboratory, Northbrook, Illinois. In addition to the experimental animals, 16 mice (four for group I, four for group II, three for group III, and five which were 12 months old) were used as controls.

To study the pulmonary effects of the chemical at smaller doses with shorter exposure, 120 mice of the same strain, sex and age were prepared. These animals were divided into four groups (30 mice in

Table 1. Pulmonary tumor production in CD1 male mice with lower doses of VC and shorter exposure (4 weeks).[a]

VC dose, ppm	1st sacrifice (immediately after dosing)	Between 1st and 2nd sacrifice	2nd sacrifice (12 weeks)	Between 2nd and 3rd sacrifice	3rd sacrifice (40 weeks)
100 (N = 30)	0/10[b]	0/4[c]	0/6[b]	0/1[c]	5/9[b]
10 (N = 30)	0/10[b]	0/1[c]	0/9[b]	0/1[c]	2/9[b]
1 (N = 30)	0/10[b]		0/10[b]	0/1[c]	1/9[b]
0 (N = 30)	0/10[b]	0/1[c]	0/9[b]		0/10[b]

[a]Reported as pulmonary tumor-bearing mice/total number of mice.
[b]Sacrificed.
[c]Found dead.

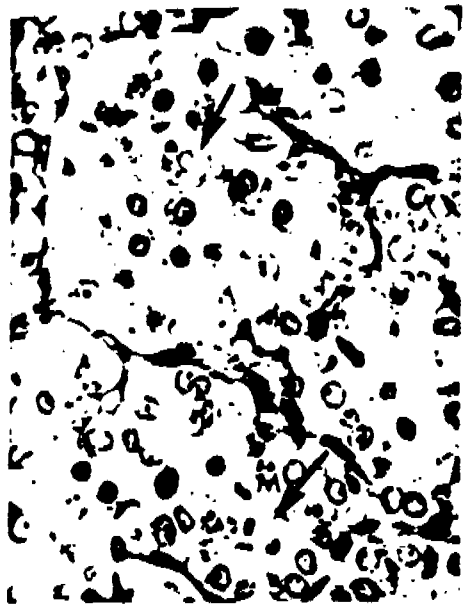

FIGURE 2. Neoplastic cells stained with PAS. An arrow indicates fine PAS-positive material digested by diastase. The arrow labeled M shows an abnormal mitosis (2500 ppm in group III). 560×.

each group) and were exposed to the chemical for 4 weeks (5 hr/day, and 5 days/week) at 100 ppm, 10 ppm, 1 ppm and 0 ppm (control). The low dose exposures were performed at the Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical U.S.A. As shown on Table 1, these animals were sacrificed at three different periods: immediately after, 12 weeks after and 40 weeks after exposure to the chemical. Six (four 100 ppm, one 10 ppm, and one control) were found dead between the first and second periods, and three (one 100 ppm, one 10 ppm and one 1 ppm) were found dead between the second and third periods.

Lungs were examined under a dissecting microscope after the organs were removed from sacrificed animals, to determine whether macroscopic abnormalities including tumor production were present.

For light microscopy, the organs were fixed in 10% neutral buffered formalin and embedded in paraffin after dehydration in alcohol. Sections (5-6 μm) were made and stained with hematoxylin–eosin, Masson's trichrome, Weigert's silver, periodic acid-Schiff's (PAS) with and without digestion by diastase, elastin and Van Gieson's picrofuchsin technique. For electron microscopy small pieces, smaller than 1 mm^3, were taken from both pulmonary tumors and nonneoplastic pulmonary tissues and were fixed in 1% phosphate-buffered osmic acid at pH 7.2-7.4 for 2 hr or in 2% paraformaldehyde fixative followed by the osmic acid. After alcohol dehydration, the blocks were embedded in epoxy resin. Ultrathin sections were obtained with an LKB microtome. The sections were stained with uranyl acetate and lead. A Siemens 101 electron microscope was used for ultrastructural observations.

Observations

Neoplastic Effects of Vinyl Chloride at Heavy Doses and Long-Term Exposures

Gross Anatomical Findings. Pulmonary tumors were observed in all experimental mice except one from the 6000 ppm series of group II (26 of 27). None were found in 16 controls. These tumors were round, whitish in color, multiple in number and variable in size from 1 to 5 mm in diameter. No metastases to regional lymph nodes or other organs were observed. Neither parenchymal fibrosis nor fibrotic adhesions of the pleura were detected.

Light Microscopy. As shown in Figure 1, the tumors were usually seen in the peripheral part of

FIGURE 3. Hyperplastic pulmonary cells are seen beneath the visceral pleura of a mouse lung (2500 ppm in group III). Hematoxylin and eosin; 430×.

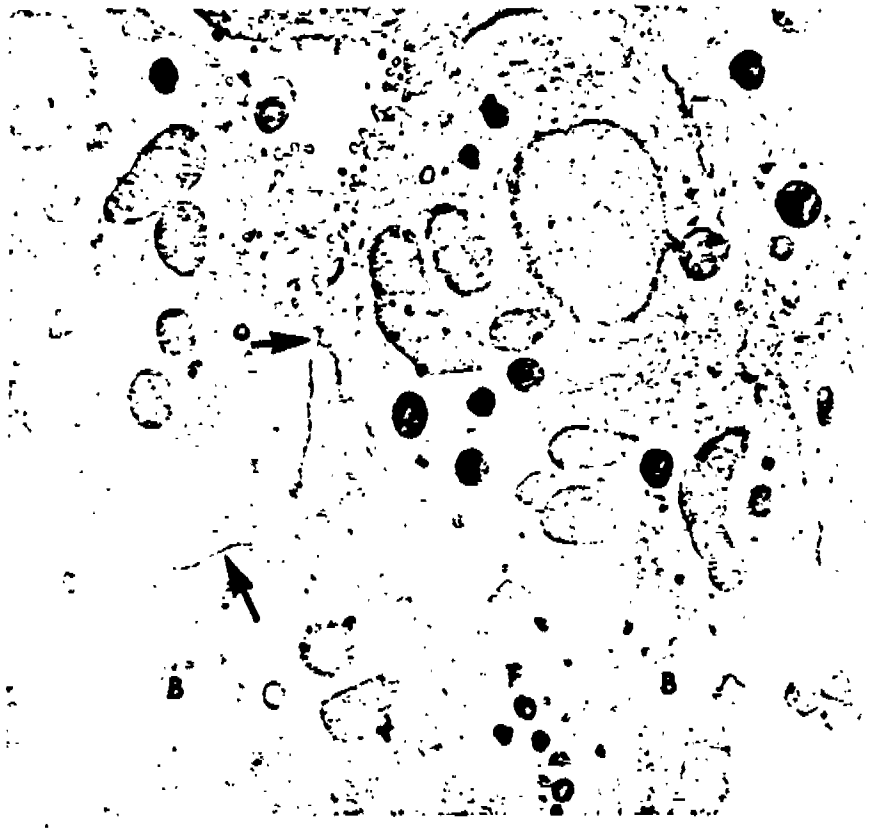

FIGURE 4. Low-power electron micrograph of a well-differentiated pulmonary tumor. Arrows indicate junctional structures between neoplastic cells. B, Basement membrane (2500 ppm in group III), OsO_4; 7900×.

lung parenchyma, although occasionally tumors were found in more proximal parts of the lung. No direct connections of the tumors with bronchi or bronchioles were observed. The neoplastic cells were arranged in various ways, such as tubulopapillary and adenomatous forms. Pleomorphism and atypical structures were not striking. However, sometimes abnormal mitoses were observed, as shown in Figure 2 (arrow labeled M). The nuclei were round in shape and small, and chromatin was generally finely distributed. Nucleoli were generally poor in development. Two different types, eosinophilic and basophilic, were distinguished in the neoplastic cells. Some of the cells stained with PAS, and the substance so stained was digested by diastase, suggesting that it was glycogen. The neoplastic tissue was not encapsulated by connective tissue. Often, air spaces separated neoplastic tissue from normal tissue. Although malignant invasion, such as destruction of preexisting tissue, was not observed in the animal lungs, invagination of the neoplastic tissue into bronchiolar air spaces was detected in instances of extremely large tumors. Collagen and reticular fibers showed little development in the neoplastic tissues. In addition to neoplastic changes, as shown in Figure 3, focal and multiple hyperplastic changes of the alveolar lining cells were noted in lungs exposed to vinyl chloride. In Figure 3, the hyperplastic cells are seen just beneath the visceral pleura. Since the lining cells beneath the thin connective tissue of the visceral pleura are known to be alveolar epithelium, the hyperplastic cells are assumed to be alveolar epithelial cells. Hyperplastic cells are also found in the deeper part of lung parenchyma. Occasionally, neoplasia and hyperplasia coexisted in the same lobe of the lung, and the distinction between neoplastic and hyperplastic cells with confidence was not always clear, as some cellular similarities were found between the two. Identification of the cell types of both

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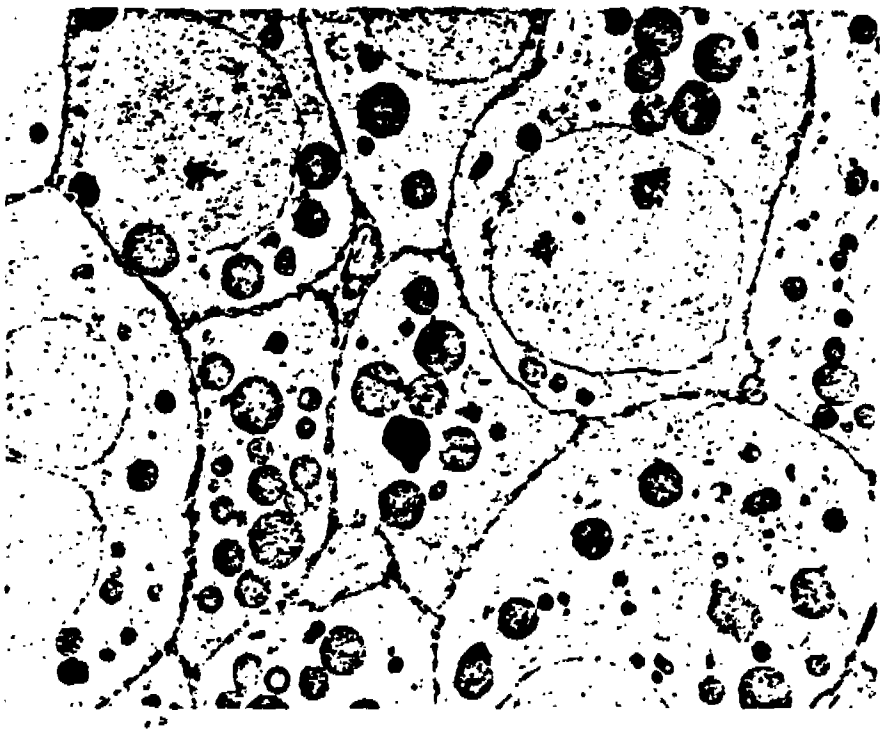


FIGURE 5. Differentiated neoplasm seen in the animal lung shown in Fig. 3. Formation of the tubular lumen and microvilli is poor. OsO_4; 6500×.

neoplastic and hyperplastic cells with confidence was not feasible at the level of light microscopy.

Electron Microscopy. Figure 4 is derived from neoplastic tissue of the tubulo-papillary form. Ultrastructural characteristics of the neoplastic cell included microvilli, large, round, or rod-shaped mitochondria, well-developed Golgi complexes, and osmiophilic lamellar bodies. Junctional structures (arrows in Fig. 4) between adjacent neoplastic cells and a basement membrane (B) were usually observed. Figure 5 was derived from an adenomatous area of the tumor. Neoplastic cells had poorly formed tubular lumens and microvilli and were smaller than those shown in Figure 4. However, other ultrastructural characteristics, such as mitochondria, Golgi complexes, and osmiophilic lamellar bodies, were almost identical in the two. Irregular arrangements of mitochondrial cristae were fairly common, and mitochondria were often wrapped by well-developed, smooth-surfaced endoplasmic reticulum (Fig. 6). Some of the neoplastic cells contained cytoplasmic compartments formed by membrane structures (Fig. 7). The occurrence of such compartments has been reported by Svoboda (*21*), who made electron microscopic observations on the neoplastic cells in mouse pulmonary tumors induced spontaneously or by urethane. Occasionally, crystalloid structures were observed in the cytoplasm of the neoplastic cells (Fig. 8). The above described neoplastic cells were quite similar in ultrastructure to type II alveolar epithelium. Capillaries in the neoplastic tissue consisted of single layers of nonfenestrated endothelium as seen in the normal alveolar capillary. In addition to well-differentiated neoplastic cells, poorly differentiated ones were also recognized (Fig. 9). As seen in Figure 9, the cells were cuboidal or cylindrical in shape and lacked formation of osmiophilic lamellar bodies. Mitochondria were small in size, although the cells were relatively rich in rough-surfaced endoplasmic reticulum. These cells seemed to correspond to the basophilic ones observed by light microscopy. Except for the lack of a large amount of glycogen, these cells resembled immature alveolar epithelium, as observed in fetal lung in late gestation. Neither cilia nor mucinous secretory granules were

FIGURE 6. Part of the cell cytoplasm of a neoplastic cell. The arrow indicates irregular mitochrondrial cristae (2500 ppm in Group III). OsO_4; 29, 400×.

FIGURE 7. Intracytoplasmic compartments formed by membrane structures (2500 ppm in group III). OsO_4; 20, 000×.

FIGURE 8. Crystalloid structure seen in the cytoplasm of a neoplastic cell (2500 ppm in group III). OsO_4; 30,000×.

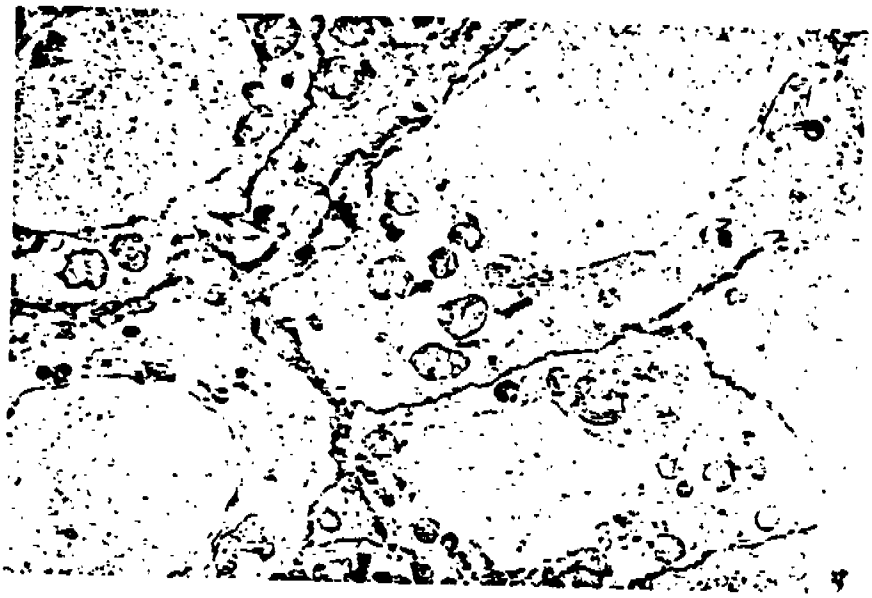


FIGURE 9. Poorly differentiated neoplastic cells. No osmiophilic lamellar bodies are observed (6000 ppm in group II). OsO_4; 5300 ×.

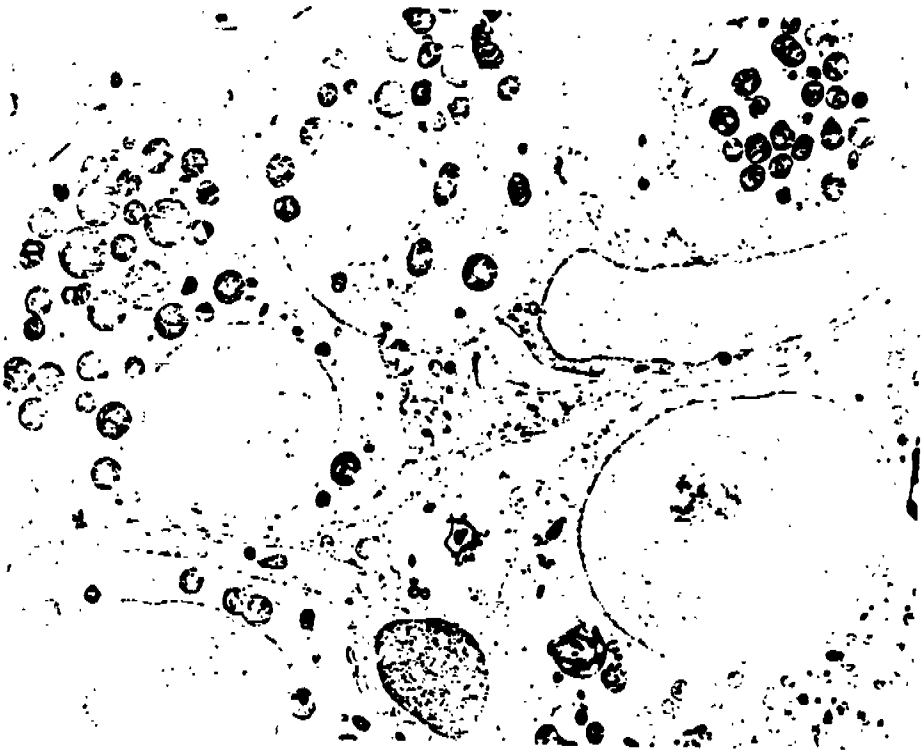


FIGURE 10. Hyperplastic type II cells are illustrated. Group 1; 6000 ppm; OsO_4; 5300 ×.

FIGURE 11. Light microscopy of a bronchiolo-alveolar area. Arrows indicate the site of transition between the respiratory bronchiole and the alveolus. Control mouse; Masson's trichrome staining; 420×.

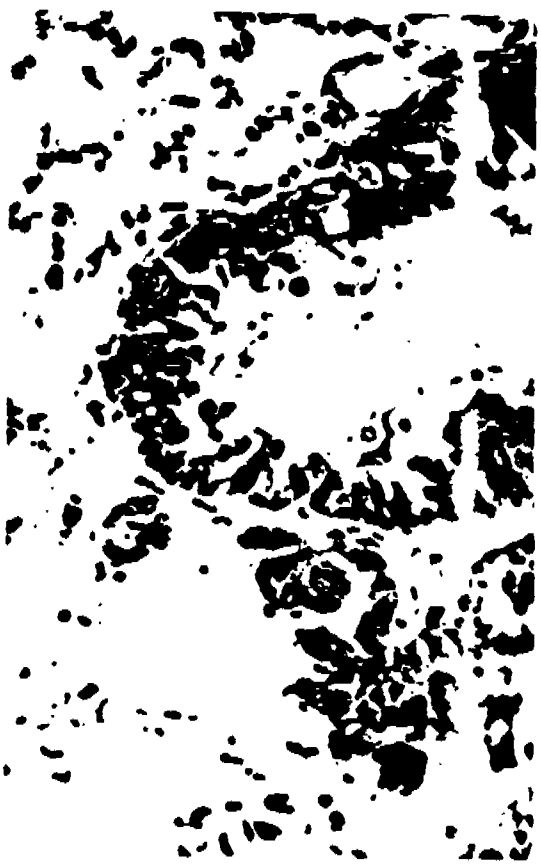


FIGURE 12. Proliferated and hypertrophic bronchioles. Desquamated bronchiolar epithelial areas are illustrated. Masson's trichrome staining; Group I; 2500 ppm, 420×.

observed in the neoplastic cells. Based on these findings, it was strongly suggested that the neoplastic cells were derived from the alveolar epithelium, particularly from type II cells. A hyperplastic pulmonary alveolus is illustrated in Figure 10. Electron microscopically, aspects of the hyperplastic cells were evidently those of type II alveolar cells, although they showed some differences in ultrastructure from the normal type II cell. Mitochondria were large in size and irregular in shape, and, occasionally, retention of huge osmiophilic lamellar bodies was noted in the cell cytoplasm. Cristae mitochrondriales were arranged irregularly, and well-developed endoplasmic reticulum was frequently seen in the cytoplasm. Early stages of the membrane formation responsible for "cytoplasmic compartments" were observed in the hyperplastic cell. In many respects, the hyperplastic type II cell is assumed to be the precursor of the neoplastic cell. An intermediate form between type I and II cells was frequently observed in the hyperplastic pulmonary alveoli. The arrow in Figure 10 indicates a part of the cell cytoplasm which may represent a transitional form between type I and II cells. Though the secretory granules were observed in the neoplastic cells, based on these findings, it was strongly suggested that the neoplastic cells were derived from the alveolar.

FIGURE 13. Hypersecretion of epithelial mucin in bronchial epithelium. Arrows indicate mucinous substance stained with PAS. Group III; 6000 ppm, 420×.

FIGURE 14. Hyperplasia of alveolar epithelium is shown. Hematoxylin-eosin: Group III: 2500 ppm; 670×.

Nonneoplastic Effects of Vinyl Chloride at Heavy Doses with Long-Term Exposure

Light Microscopy. In the bronchi and bronchioles, as a common finding in the treated animals, proliferation and hypertrophy of the bronchiolar epithelium were noted. As shown in Figure 11, the terminal and respiratory bronchioles of the control mice were relatively simple in structure and the transitional point (arrows) of the respiratory bronchiole into the alveolus was easily distinguished. To differentiate the two areas, we found that Masson's trichrome was a useful stain, since the cytoplasm of the bronchiolar cells was stained an intense brown red. The bronchioles of all the animals treated with vinyl chloride monomer showed proliferation, and cellular hypertrophy, through the degree varied among the animals (Fig. 12). The proliferated cells were irregular in arrangement (Fig. 12). Frequently, hypersecretion of epithelial mucin in goblet cells of the bronchi as well as the proximal bronchioles was observed (Fig. 13, arrows). It was noteworthy that those alterations were still found in the animals of group III, which had a recovery time of 37 days after vinyl chloride exposure. Chronic inflammatory changes represented by marked lymphocyte infiltration into the perivascular and peribronchiolar connective tissue were seen, particularly in group III.

The most significant finding in pulmonary alveoli was a high incidence of alveologenic tumors in the treated mice, as stated before. In addition to the neoplasm, multiple foci of hyperplastic alveolar epi-

FIGURE 15. Large clear macrophages (foam cells) as well as small basophilic macrophages are seen in the alveolar air spaces. Hematoxylin-eosin: Group III: 2500 ppm; 420×.

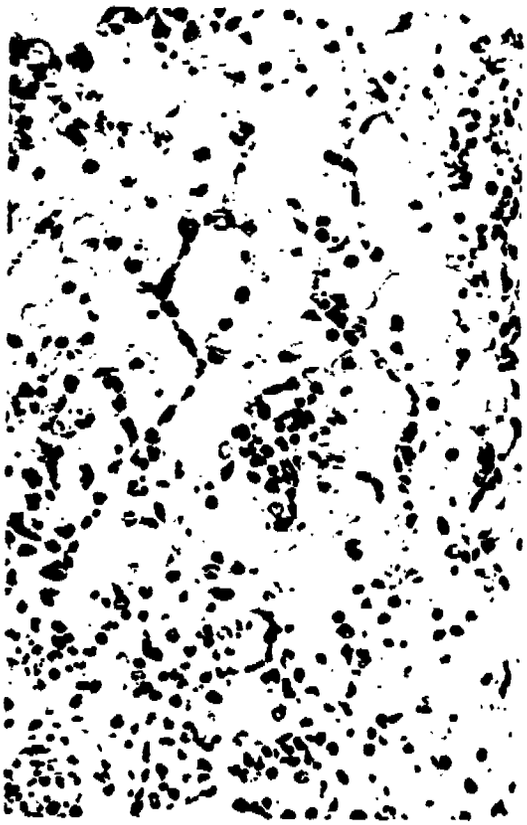
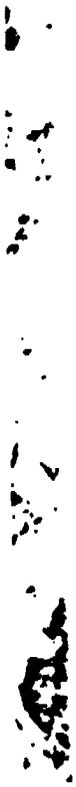


FIGURE 16. Striking accumulation of a large number of foam cells. Hematoxylin-eosin: Group III: 6000 ppm; 420×.



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thelium (Fig. 14), which were strongly suggestive of being preneoplastic for alveologenic tumors (22), were frequently observed. Mobilization of alveolar macrophages in the alveolar space was fairly commonly seen in the three groups of animals (Fig. 15). In several cases, foam cells were markedly accumulated in alveolar space (Fig. 16). Two animals in group III showed bronchopneumonia-like changes. As shown in Figure 17, coexistence of the proliferated bronchioles with alveologenic tumors (arrow) was frequently observed.

Electron Microscopy. The epithelium of the terminal bronchiole consists of the Clara cell (nonciliated) and ciliated cells; it lacks mucous-producing cells in the mice. Both cell types are illustrated in Figure 18, obtained from a control mouse. Clara cells lack typical microvilli and their apical portion present a dome-like shape (Fig. 18). The smooth-surfaced endoplasmic reticulum and Golgi complex were well developed. Mitochondria were generally round in shape and their cristae were few in number (Fig. 18). Two distinct granules, a beadlike structure (electron-dense; the long axis was 1.6-0.2 μm) and a round phagolysosomal granule (electron-dense or opaque; 0.6 × 0.6 μm in size) were observed in the cells. It is noteworthy that the ultrastructure of the cell is not identical among animal species and, further different fixation methods result in different structural appearances of the endoplasmic reticulum in the cell.

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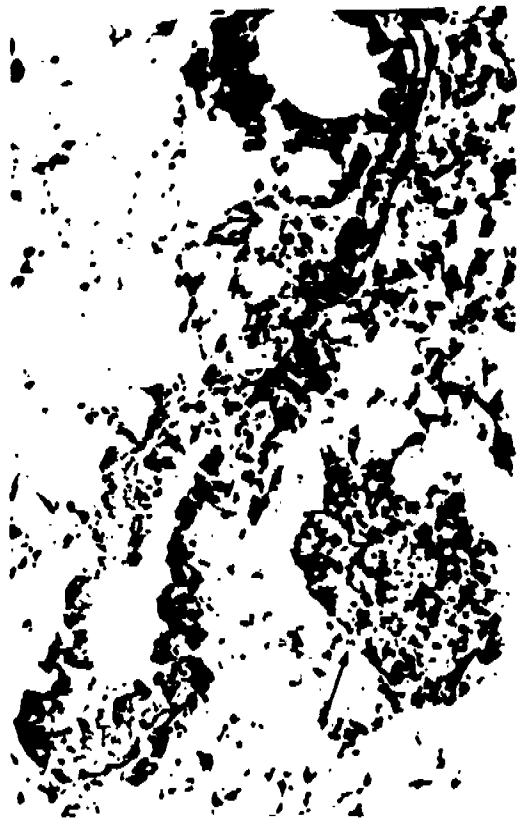

Part of lung tissue showing coexistence of the alveolar cell tumor (arrow) with the proliferated bronchiole. Masson's trichrome staining; Group I: 6000 ppm; 170×.

The cytoplasm of the ciliated cell was relatively clear and it contained rod-shaped mitochondria with cristae (Fig. 18). Cilia and microvilli were seen in the cell surface (Fig. 18). The two distinct granules were also occasionally seen in the cell. Ultrastructural changes seen in those cell types of the treated mice are described below.

A low-power view of the proliferated bronchiole is illustrated in Figure 19. Hypertrophic Clara cells frequently included dark cells rich in rough-surfaced endoplasmic reticulum and free ribosomes. The cell was usually large and its shape was occasionally irregular. Deep interdigitation of the lateral cell membranes of two adjacent cells was occasionally observed. Golgi complexes were well developed, and the two distinct granules described above were increased in number in the cytoplasm. The dark round granules are shown in Figure 19. Although smooth-surfaced endoplasmic reticulum of the normal Clara cell was generally vesicular (with a single osmic acid fixation as used in this study, though this cell organoid is cisternal with double fixation by glutaraldehyde and osmic acid), the hypertrophic cells contained various forms of the organoid and the transformation of the rough surfaced endoplasmic reticulum into smooth-surfaced endoplasmic reticulum was easily observed (Fig. 20). Mitochondria of abnormal shapes and large size occasionally appeared. Cristae were rather clearly shown in such abnormal mitichondria (Fig. 21).

Ciliated cells were also involved in the proliferated alteration. The shape of the cells was occasionally irregular. Golgi complexes were sometimes well developed and phagolysosomal granules as well as round dense granules frequently appeared in the cytoplasm (Fig. 22). Large round mitochondria in which cristae were fewer in number were seen. In some ciliated cells, the rough and smooth surfaced endoplasmic reticulum were markedly developed (Fig. 22).

Although light microscopic observations failed to detect details of damages in the pulmonary alveolus, various ultrastructural alterations of the alveolar cells were revealed by electron microscopy.

Mobilized alveolar macrophages were rich in phagolysosomal granules, as shown in Figure 23. Other cell organelles were also well developed. Basophilic macrophages contained a large number of free ribosomes as well as the rough-surfaced endoplasmic reticulum, while clear macrophages were represented by intracytoplasmic osmiophilic lamellar bodies (Fig. 23) which seemed to be phagocytosed from the alveolar space. Occasionally, cholesterol crystalloids were found in the macrophages (Fig. 24, arrows).

As shown in Figure 10, hyperplastic alveolar epithelium consisted of type II cells, precursors of alveolar tumor (*15*). The evolutional process of the neoplastic transformation has been reported (*15*). Deformation of the cell shape, appearance of giant mitochondria with abnormal cristae, retention of large osmiophilic lamellar bodies, early introcytoplasmic "sequestration," and occasional huge lipid granules were observed. Microvilli of the cell surface were frequently decreased in number. These alterations were observed in almost all mice exposed to vinyl chloride, regardless of difference in dose and duration of recovery time.

Swelling of the cytoplasm and appearance of lysosomal granules were occasionally observed in type I cells. Transformation of the type I cells into the

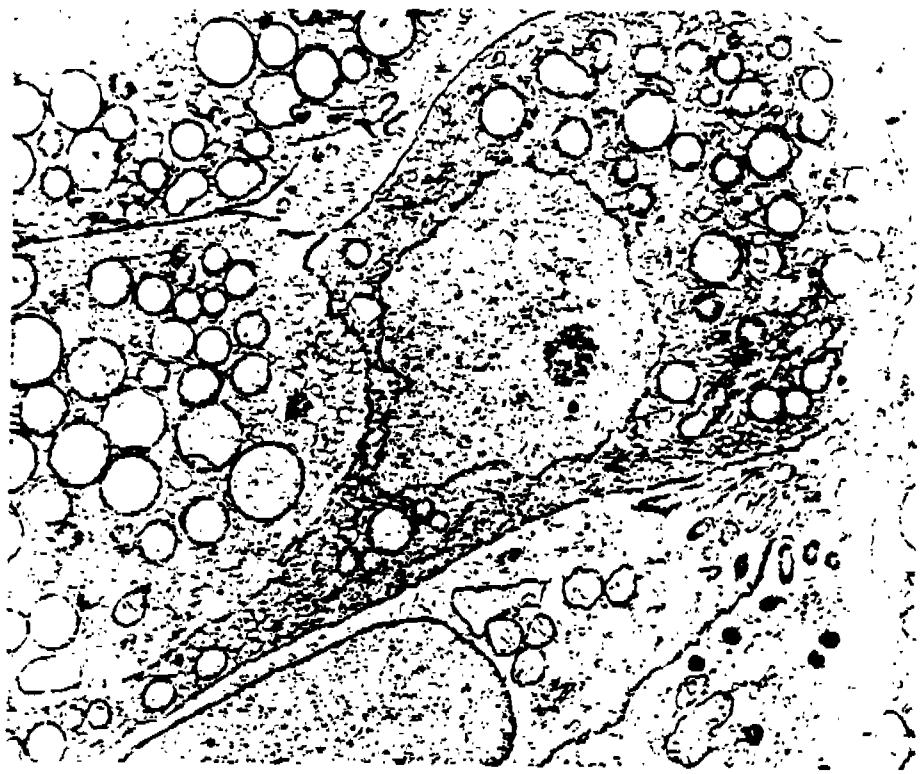

FIGURE 18. Part of the terminal bronchiole. Clara cells and ciliated cells are illustrated. Control mouse; OsO_4; 6700×.

type II cells was suggested, since intermediate cell types between the two were found on the alveolar lining.

Focal thickening of the basement membrane was commonly seen (Fig. 25). Sometimes, the thickened basement membrane showed a fibrillar appearance ("f" in Fig. 26) and contained cell debris (arrows in Fig. 26) which seemed to be derived from alveolar septal cells.

In addition to swelling of the cytoplasm, lysosomal granules and a large nucleus (Fig. 27), segmented or nonsegmented, were sometimes observed in the alveolar endothelium.

Alveolar septal cells frequently showed hypertrophy (h in Fig. 28) and degeneration (arrows in Fig. 28). In some cases, focal reticulosis was observed in the alveolar septum.

From these light and electron microscopic studies, mouse lungs exposed to vinyl chloride at 2500 and 6000 ppm for 5 and 6 months clearly showed nonneoplastic pulmonary changes in both bronchiolar and alveolar cells. Since these findings were not detected in control mice, they are considered related to vinyl chloride.

Neoplastic Effects of Vinyl Chloride at Smaller Doses with a Shorter Exposure

Detailed studies on pulmonary effects of vinyl chloride at smaller doses (1, 10 and 100 ppm) with a shorter exposure (4 weeks, 5 hr/day, 5 days/week are still in a process of analyses in 90 mice. However, as shown in Table 1, our preliminary study that involved gross anatomical and histological observations revealed that alveologenic tumors were induced in 5 of 9 (100 ppm), 2 of 9 (10 ppm) and 1 of 9 (1 ppm), while the tumor was not seen in 10 control

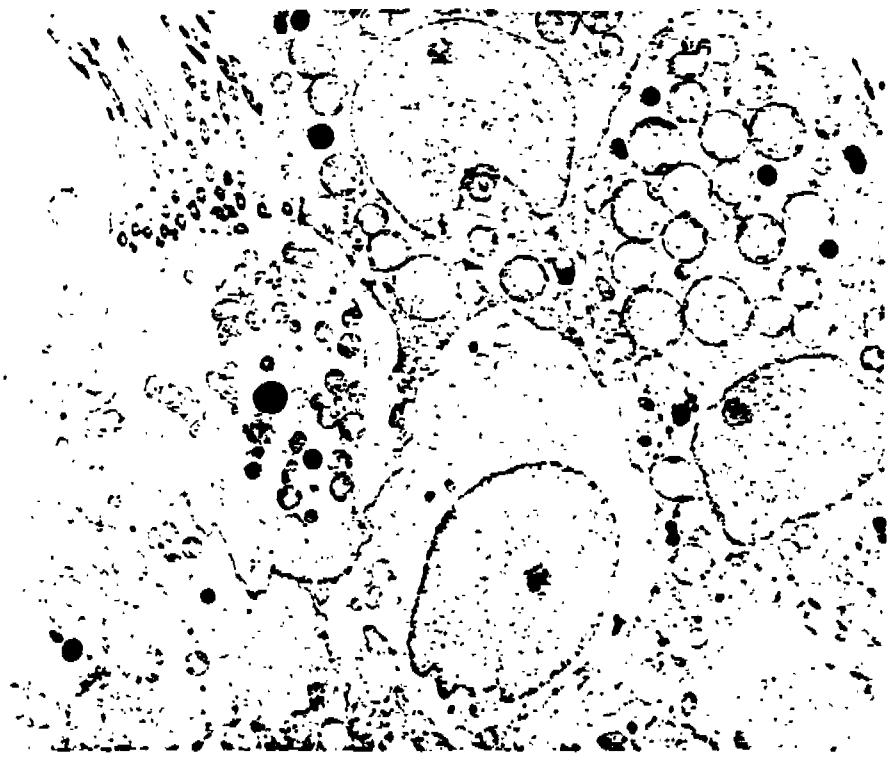

FIGURE 19. Proliferated bronchiolar epithelium. Group I: 6000 ppm; 3300 ×.

(0 ppm) at 40 weeks after vinyl chloride exposure. Size and number of the induced tumors were generally smaller than those of the tumors produced by the chemical at larger doses (2500 ppm and 6,000 ppm) and longer exposure (5 and 6 months).

A dose response relation was suggested in production of alveologenic tumor.

Discussion

Experimental studies (*10-17*) on the oncogenicity of vinyl chloride have revealed that the monomer can induce various neoplasms including hepatic hemangiosarcoma (rat, mice, hamsters), Zymbal gland carcinoma in the external auditory meatus (rats), breast cancer (mice), nephroblastoma (rats), "lung adenoma" (mice), skin trichoepithelioma (hamsters), lymphoma (hamsters) and forestomach papilloma (hamsters). Evidence of the pulmonary oncogenicity of vinyl chloride in animals has been obtained. Viola et al. (*16, 17*) have reported that rats exposed to vinyl chloride exhibited lung cancer (32%). Histological features of the cancers were stated to be those of adenocarcinoma, with the exception of a single epidermoid tumor. Maltoni and Lefemine (*13,14*), however, reviewed the histological slides of Viola et al. and stated that the lung cancers reported by the latter were not primary tumors of the lungs, but metastatic cancers from Zymbal glands. Maltoni and Lefemine (*13,14*) also have reported on the pulmonary oncogenicity of vinyl chloride on the basis of their own data. Though they could not find bronchogenic carcinoma in rats, rare pulmonary hemangiosarcomas and fibrosarcomas were induced in these animals. Unlike the case in rats, pulmonary tumors ("adenomas") were found in mice (89 of 471). Maltoni and Lefemine (*13,14*) noted that some of the adenomas underwent malignant transformation. Keplinger and associates (*11*) have found "alveologenic adenomas" in the lungs of mice exposed to vinyl chloride (44 of 49). Lee and associates (*12*) have stated that "bronchiolar ade-

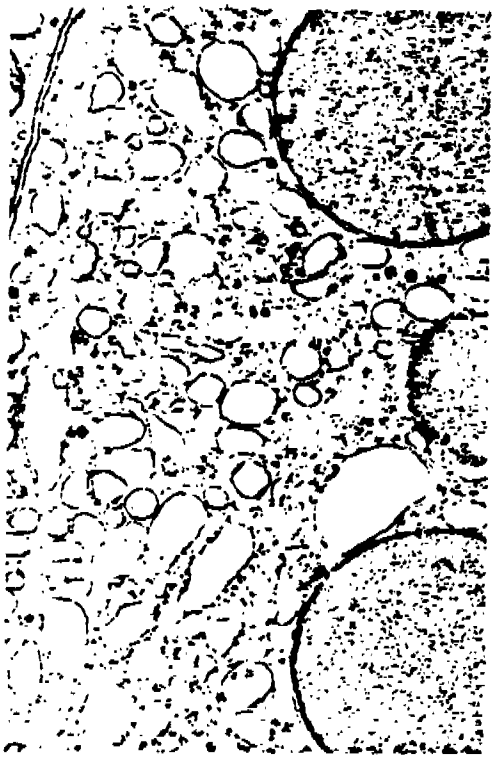

FIGURE 20. Part of the cytoplasm of a Clara cell. Various profiles of the endoplasmic reticulum are seen. Group I: 2500 ppm; 21,000 ×.

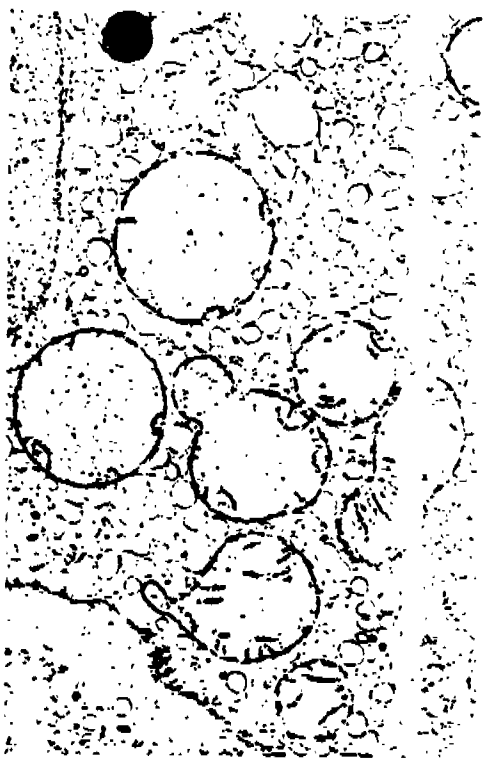

FIGURE 21. Irregular shaped mitochondria with cristae in the cytoplasm of a Clara cell. Group I: 6000 ppm; OsO_4; 12,600 ×.

noma" developed in mice 2 months after exposure to vinyl chloride at 50-1000 ppm. Holmberg and associates (*10*) found "alveologenic adenoma" in 13 of 24 mice exposed to vinyl chloride at 50 ppm for 24-52 weeks. Our present study has also confirmed that pulmonary tumors are induced by vinyl chloride of both the large doses (2,500 and 6,000 ppm) with long exposure (5 and 6 months) and the smaller doses (1, 10 and 100 ppm) with a short exposure (4 weeks).

Based on all the data available, it can be concluded that mouse lung is an extremely sensitive organ for demonstrating the oncogenicity of vinyl chloride. Gross anatomical and histological aspects of the tumors in our investigation corresponded to the "alveologenic tumor or cancer" of Steward et al. (*22-24*). The alveologenic tumor has been induced by various carcinogens (*22-28*), such as polycyclic hydrocarbons, urethane, nitrogen mustard, methylcholanthrene, and nitrofur derivatives and is known to occur spontaneously with aging (*6,29,30*). The cancer induced has been distinguished from that occurring spontaneously by multiple primary foci, occasional formation of huge tumors, and occurrence without any relation to aging. It is also known that in certain strains, such as A and DD, spontaneous tumors are quite common after 10 to 12 months of age. Spontaneous pulmonary tumors could be excluded in our experimental animals; in addition to the above-mentioned points, neoplastic changes in the lungs were absent in the controls.

Electron microscopically, alveolar epithelium, particularly the type II cell, was assumed to be the precursor of vinyl chloride-induced tumor in the mouse lung. This assumption was derived from ultrastructural similarities between the normal type II cell and the neoplastic cell. Similar suggestions have been made by other investigators (*21, 28, 31*) after studying pulmonary tumors induced by agents other than vinyl chloride.

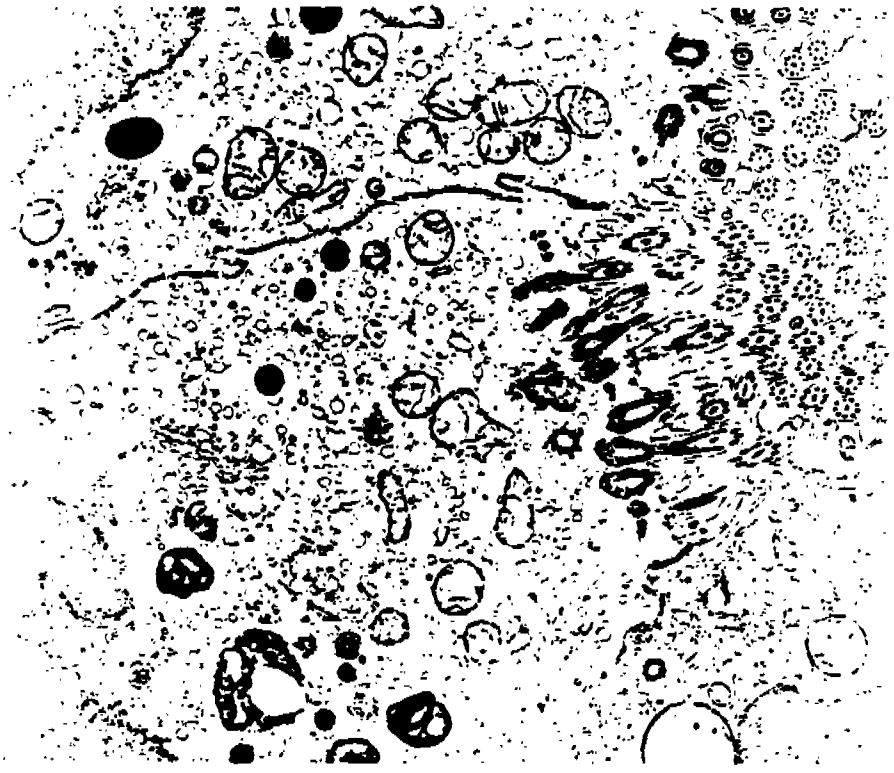

FIGURE 22. Two ciliated cells of a terminal bronchiole. Irregular shaped mitochondria, a well developed Golgi area, round dense granules and phagolysomes are shown. Group I: 6000 ppm; OsO_4; 9800×.

It was noteworthy that the processes of transformation of the normal alveolar epithelium into the neoplastic cell could be followed morphologically on the level of ultrastructure; the appearance of an intermediate form between type I and II cells in the alveolar lining, the disappearance of type II cell in the lining due to replacement by the hyperplastic type II cells, which were transformed from the intermediate form, and the neoplastic change of the type II cells were assumed to be a sequence of the process. The intermediate form appears in certain pathological conditions, prior to cuboidal metaplasia of the attenuated alveolar epithelium (*15*, *32*). Embryologically, both type I and II cells are of the same origin, the entodermal epithelum. Some of the neoplastic cells, distinguished as poorly differentiated, were similar in ultrastructure to the immature alveolar epithelium of fetal lung (*15*). From these perspectives, the process of neoplastic alteration observed in the epithelium may be interpreted as a retrograde process of the normal differentiations of the alveolar epithelium. Kaufman et al. (*33*) have reported that Clara cells of the mouse bronchioles developed into neoplasms which could occur in a malignant form, after transplacental exposure to ethylnitrosurea. However, such a Clara cell tumor was not produced in our material.

Waxweiler and associates reported an increased number of deaths due to lung cancer among vinyl chloride workers (*9*). They observed 12 cases compared to the 7.7 cases expected. Eight of the twelve were examined histologically and were classified as undifferentiated large-cell carcinoma (five cases) and adenocarcinoma (three cases). Since these human lung cancers are of bronchogenic origin, it may be that target pulmonary cells in vinyl chloride carcinogenesis are different in human and mouse lung.

Neoplastic invasion and metastases were not found in our material. However, it is known that sometimes both induced and spontaneous alveologenic

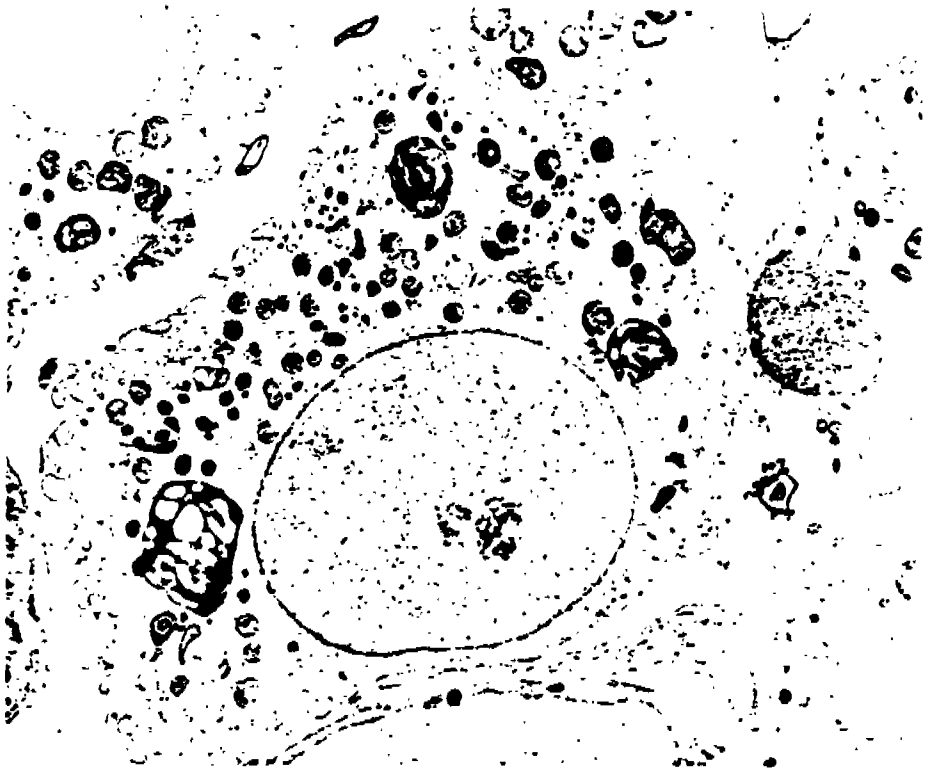

FIGURE 23. Alveolar macrophage including phagolysosomes and osmiophilic lamellar bodies. Group I: 2500 ppm; OsO_4; 5800 ×.

tumors (*22*, *34-37*) of mice show such changes and that the malignant transformation occurs with some delay after initiation of the tumor. In addition, transplantation of this tumor has been accomplished (*23*). Steward and associates (*22-24*) therefore dubbed it an "alveologenic tumor" or "alveologenic cancer." Maltoni and Lafemine (*13,14*) have found that some vinyl chloride-induced pulmonary tumors undergo transformation, although we did not observe this in our materials.

Alveologenic tumors may be considered unique in some ways, since it is possible to observe the process of malignant transformation sequentially from the precursor to the malignant cell via hyperplastic and benign neoplastic states.

Hepatic hemangiosarcoma is recognized as a characteristic malignant tumor related to vinyl chloride exposure. The tumor can be induced in a variety of experimental animals (mice, rats, and hamsters) (*13,14*), and histological features of the tumor are almost identical in humans and animals. In contrast, the intrapulmonary target cells of vinyl chloride oncogenesis may be different in humans and mice. Beyond these differences, moreover, the induction of alveologenic tumors in mice by vinyl chloride may be predictive or a risk of human bronchogenic cancer from the chemical. Consistent with this is the fact that various carcinogens, such as polycyclic aromatic hydrocarbons, nitrogen mustard and chromate compounds, are known to induce alveologenic tumors in mice, on one hand, and, on the other, to be associated with excess bronchogenic carcinoma among workers exposed to the carcinogens (*38*). It is noteworthy that a similar relation has been suggested for vinyl chloride.

Nonneoplastic pulmonary effects of vinyl chloride

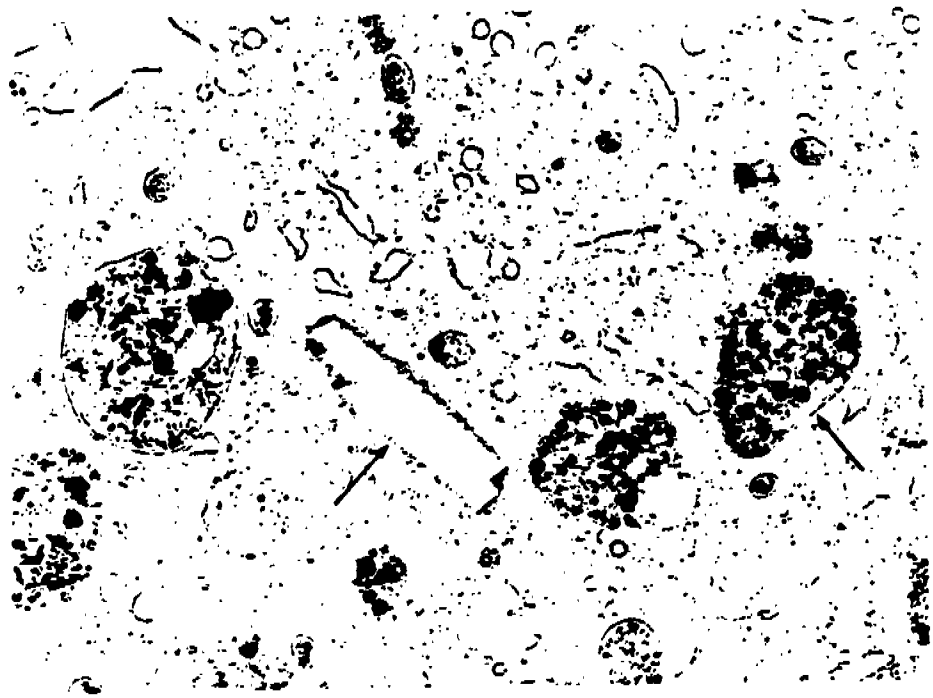

FIGURE 24. Part of a macrophage. Two cholesterol crystalloids are shown. Group III: 2500 ppm; OsO_4; 27,000 ×.

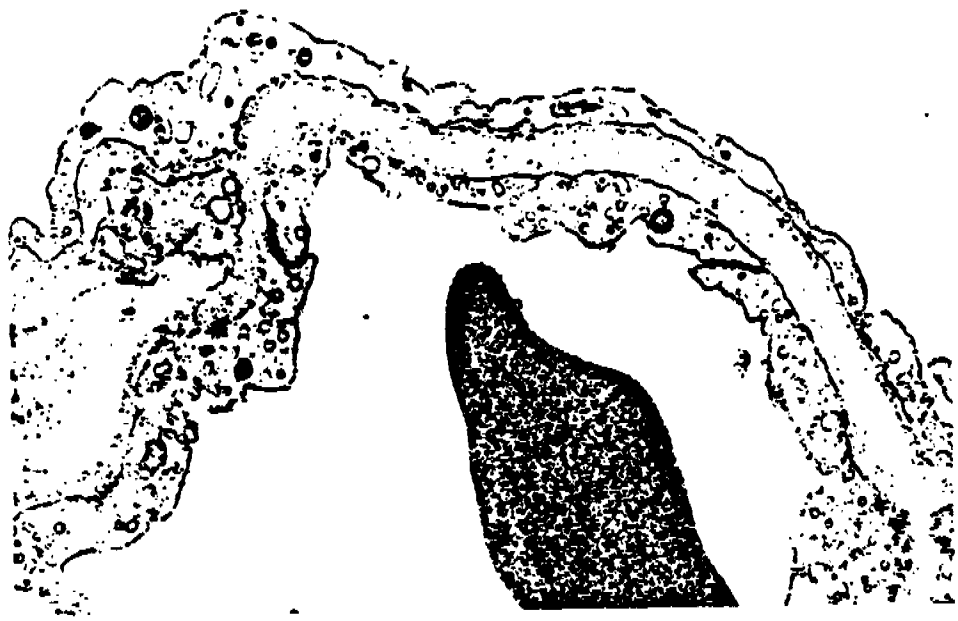

FIGURE 25. Thickened basement membrane of an alveolar capillary. Group I: 6000 ppm; OsO_4; 15,000 ×.

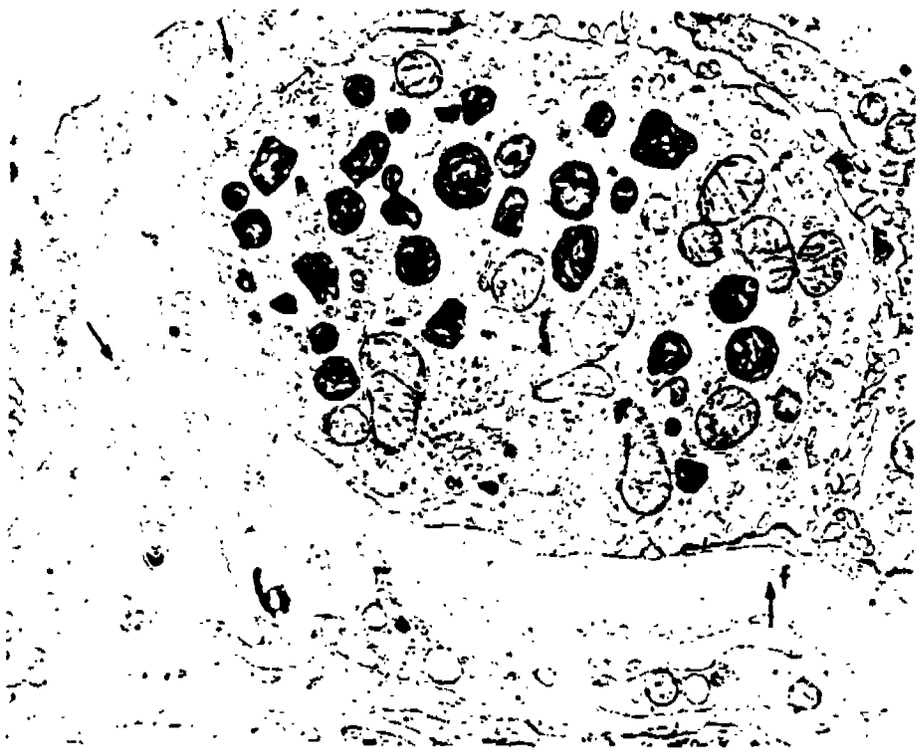

FIGURE 26. Cell debris of degenerated alveolar septal cells (arrows) and fibrillar appearance of a basement membrane (with an arrow) are illustrated. Group 1: 6000 ppm; OsO_4; 10,300×.

have been suggested by observations among workers in vinyl chloride polymerization plants. This suggestion was based on data obtained by chest x-ray examinations, pulmonary function tests, and sputum cytology studies among workers. Lilis and her associates (*18*) have found radiologic pulmonary changes, such as linear, reticular, and nodular opacities, in the lower and mid lung fields in a proportion of cases. They found that the prevalence of pulmonary changes increased with longer duration of exposure and that there was a significant association with peripheral circulatory abnormalities. However, pathological evaluation of these changes was not available. Miller et al. (*19*) have examined pulmonary function of 348 workers in a vinyl chloride polymerization plant. The major finding was diminution of air flow in 200 workers (57.7%). Again, no physicopathological relations were established. Maltoni and Lefemine (*14*) reported cytological studies of sputum in vinyl chloride and poly(vinyl chloride) workers. They found a significant increase in cellular changes of the bronchial epithelium; squamous metaplasia and squamous dysplasia were common among workers heavily exposed to vinyl chloride monomer.

Recently, McNamara and McLaughlin (*39*) have confirmed that a single 1-hr exposure to vinyl chloride in doses of 500 ppm or more induced pneumonitis in ICR mice and that aggravation of latent pulmonary changes, particularly bronchopneumonia, occurred in Fischer 344 rats.

Our present (*40*) study has shown that CD1 Charles River male mice exposed to vinyl chloride at a heavy dose (2500 and 6000 ppm), over relatively long term (5 and 6 months), obviously showed bronchiolo-alveolar changes. These alterations were recognized in almost all of the treated animals regardless of difference in doses (2500 and 6000 ppm), duration of exposure (5 and 6 months) and recovery time (2, 6 and 37 days).

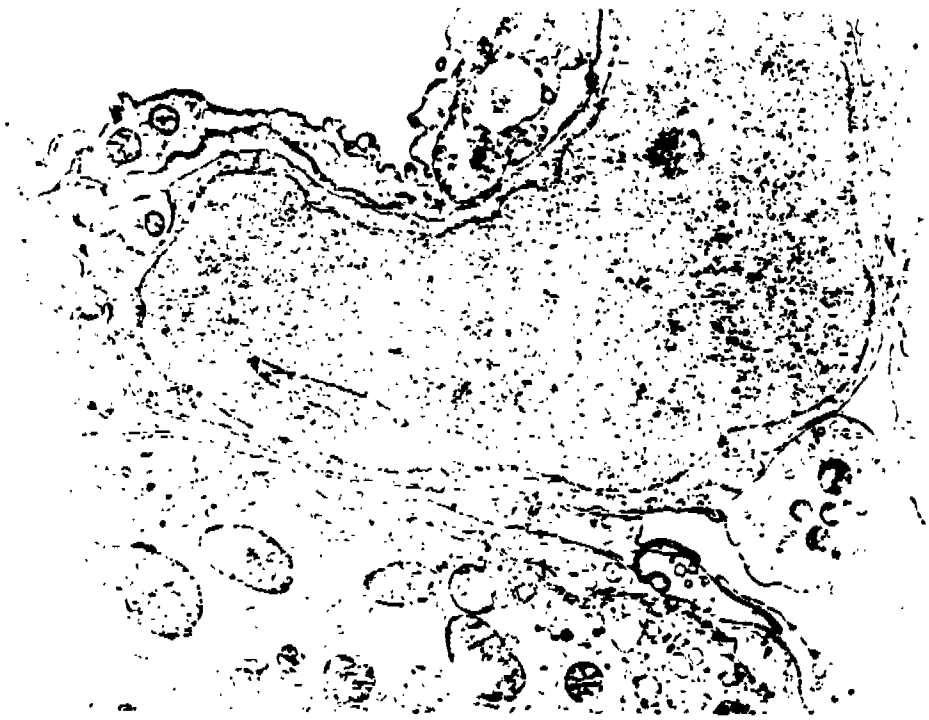

FIGURE 27. Large nucleus in the alveolar capillary endothelium. Group II: 2500 ppm; OsO_4; 7900×.

The types of pulmonary cells which were involved in the structural alterations varied. It was interesting that the ultrastructural changes seen in Clara cells and to some extent in the ciliated cells were similar to those of hepatic cells of animals exposed to vinyl chloride; cellular hypertrophy and proliferation of the endoplasmic reticulum were common responses, seen in both the bronchiolar epithelium and the hepatic cells. The endoplasmic reticulum of the hepatic cells has been suggested as the site where vinyl chloride is metabolized, to be transformed into a chemically reactive metabolite which is the ultimate carcinogen (*36*, *41-45*). Although it has not been shown that lung has the capacity to metabolize the chemical to produce the carcinogen; if it were so, the bronchiolar cells, particularly Clara cells, may provide this mechanism: the cells are normally equipped with well-developed smooth-surfaced endoplasmic reticula and the organelles have shown a proliferative response after mice are exposed to vinyl chloride.

The fact (*46*) that vinyl chloride has a tendency to be soluble in lipid substances suggests that lipid-rich pulmonary cells, such as type II cells (rich in osmiophilic lamellar bodies) and alveolar septal cells (containing lipid granules) may bind to vinyl chloride. If this assumption is correct, at least some of ultrastructural alterations seen in those cells might result from this mechanism. Both type II cells and Clara cells have been known as surfactant factor-producing cells (*47*). Hyperproduction of the surfactant factor was suggested, since hyperplasia of those cells was commonly seen in our material. Osmiophilic lamellar bodies and cholesterol crystalloids, which were seen in alveolar macrophages, may represent lipid substances bound to vinyl chloride. They may be removed from lung as part of the clearance mechanism for vinyl chloride. It is well accepted that mesenchymal elements such as bone, connective tissue, and blood vessels are involved in responses to vinyl chloride in various organs (*36*, *48-50*). Above all, malignant transformation of the blood capillary endothelium, induction of hemangioendothelioma in liver, and the subcutaneous con-

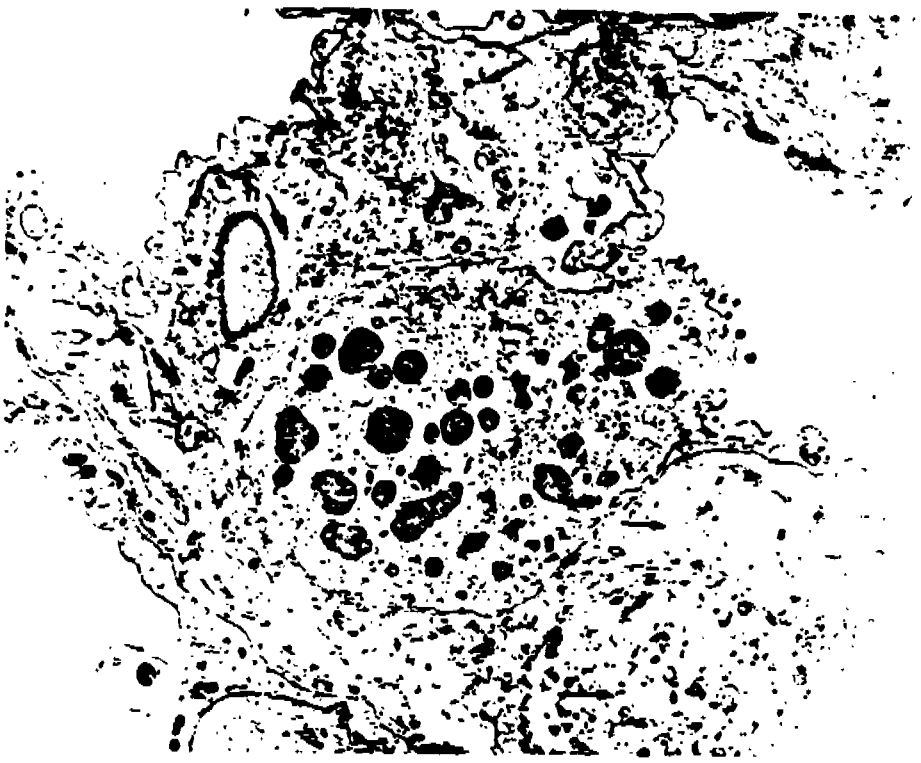

FIGURE 28. Degenerative alterations of the alveolar septal cells (arrows) and a hypertrophic septal cell (h with an arrow). Group I; 6000 ppm; OsO_4; 6300×.

nective tissue, lung, and adipose tissue have been well documented (*10*, *13*, *14*, *36*).

It is reasonable to assume that the alveolar capillary endothelium and the septal cell suffered toxic effects by vinyl chloride, since these cells are part of the mesenchymal elements in lung, sites of uptake and excretion of the chemical and its metabolites (*51*, *52*).

A dose-response relationship has been suggested in the production of alveolongenic tumors by vinyl chloride. The same relationship has been seen in occurrence of alveolitis (mouse) and bronchopneumonia (rats) with the chemical (*39*). A delayed appearance of these inflammatory changes after periods of recovery, following exposure to the chemical, has been postulated. A threshold dose for the induction of the nonneoplastic pulmonary lesions which are reported here has not been established.

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Effects of Aging on the Induction of Angiosarcoma

by David H. Groth,* William B. Coate,†
Borge M. Ulland† and Richard W. Hornung‡

Adult, Sprague-Dawley albino rats of four different ages (6, 18, 32 and 52 weeks) were exposed to 940 ppm vinyl chloride by inhalation for 24 weeks, 5 days/week, 7 hr/day. In each age group, there were 110 to 128 males and the same number of females. The similarly housed control group, which was not exposed to vinyl chloride, consisted of the same number of males and females in each age group. All animals that died spontaneously, or were sacrificed moribund, or were killed at scheduled times (3, 6 and 9 months after initial exposure) were autopsied. All organs were examined grossly, and several tissues from each animal were examined microscopically.

The older the rats were when they were first exposed, the greater the incidence of angiosarcomas. The incidences of angiosarcomas in the four age groups (from youngest to oldest) in the exposed males in the nonscheduled sacrifice groups were: 0/37 (0%); 0/44 (0%); 3/45 (6.7%); and 13/55 (24%). Similarly, for the females, these incidences were: 2/38 (5.3%); 7/47 (15%); 23/49 (47%); and 11/54 (20%). Most of the angiosarcomas were highly anaplastic, primary tumors in the livers that metastasized to the lungs. Only one angiosarcoma was seen in all the control rats; that occurred in subcutaneous tissue.

This study demonstrated that older adult animals and females are more susceptible to the angiosarcoma-inducing effects of vinyl chloride than young adult animals and males, respectively.

Introduction

Several epidemiological studies performed on occupational groups exposed to carcinogens have shown greater increased risks of cancer with increasing exposure durations. In addition, latent periods (time between initial exposure and increased risk of cancer) in these groups are commonly 10-30 years. These findings have been commonly attributed to greater total doses in those exposed for longer periods of time. However, there is one factor other than the total dose which could be responsible for contributing to the increased risk. That factor is aging. It is equally reasonable to postulate that older adults are more susceptible to the carcinogenic effect of some chemicals than young adults. That is, for the same dose of carcinogen, the incidence of cancer might be higher and the latent period shorter in older adults than in younger adults.

It has been suggested that only older people should work in carcinogenic environments, since the commonly observed latent periods for cancer induction would exceed their life expectancies. If, however, the latent periods were shorter in older individuals, that approach would be counterproductive.

The purpose of this study was to determine whether or not older adult rats were more or less susceptible to the angiosarcoma-inducing effects of vinyl chloride than young adult rats. This experiment was not designed to test the susceptibility of sexually immature animals or to determine the lifetime effect of relatively short-term exposures.

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Materials and Methods

A total of 473 male and 478 female Sprague-Dawley rats were exposed to 948 ppm of vinyl chloride monomer in a single 14 × 13 × 10 ft stainless steel walk-in chamber with a diffusion-screen false ceiling. Exposures were for 7 hr/day, 5 days/week for a mean duration of 24.5 weeks. An equal number of control male and female rats, kept in a similar exposure chamber, were exposed to conditioned outside air only. Air flow into the chambers was maintained at 300 ft^3/min. Air temperatures were kept at 75 ± 3°F. The concentration of vinyl chloride in the chambers was initially monitored by gas chromatography and later with an ultraviolet photoionization analyzer, 7 times/day on each day of exposure.

The animals were individually housed in suspended stainless steel wire-mesh cages equipped with automatic watering taps. Water was provided *ad libitum*, but food (Wayne Lab Blox) was removed during exposures.

Four differently aged sets of rats of both sexes were used in both the exposed and control groups. Their ages at initiation of exposure were 6, 17-18, 32-33 and 51-53 weeks. The numbers in each group and their disposition appear in Tables 1 and 2.

Because of the large number of animals, it was not practical to start exposures on all rats simultaneously. Consequently, the controls and exposed rats were divided into five squads, with proportionate representation of each age group and sex in each squad. Rats in each squad were assigned to the chambers over a 2-week period. Assignments of all rats to the chambers were completed throughout a 10-week period.

The original plan was to expose the rats for 12 months, but because of an epidemic of pneumonia among the exposed animals during the 28th week, the exposures were terminated 29 weeks after initiating exposures. As the results will show, this exposure period was adequate to demonstrate the differences in effects between groups.

The experiment consisted of two subsets. Animals scheduled for sacrifice at 3, 6 and 9 months constituted one subset, and animals that died o

Table 1. Number and disposition of rats exposed to vinyl chloride.

Group	Age at first exposure, weeks	Mean body weights at first exposure, g	Sex	Initial number of rats	Number of deaths and moribund sacrificed	Number at final sacrificed	Number sacrificed at 3, 6 and 9 months	Total number of rats autopsied
2	6	228	M	110	36	6	66	108
2	6	167	F	110	16	23	70	109
4	17–18	541	M	119	39	13	67	119
4	17–18	304	F	120	33	16	70	119
6	32–33	693	M	116	43	4	69	116
6	32–33	350	F	120	45	6	69	120
8	51–53	739	M	128	60	0	67	127
8	51–53	375	F	128	52	6	70	128
Totals			M	473	178	23	269	470
			F	478	146	51	279	476

Table 2. Number and disposition of control rats.

Group	Age at first exposure, weeks	Mean body weights at first exposure, g	Sex	Initial number of rats	Number of deaths and moribund sacrificed	Number at final sacrificed	Number sacrificed at 3, 6 and 9 months	Total number of rats autopsied
1	6	230	M	110	9	6	69	84
1	6	178	F	110	6	23	71	100
3	17–18	550	M	119	11	18	70	94
3	17–18	304	F	120	9	16	70	95
5	32–33	701	M	115	12	4	70	86
5	32–33	353	F	120	10	6	69	85
7	51–53	772	M	128	23	0	70	98
7	51–53	385	F	127	27	6	69	102
Totals			M	472	55	28	279	357
			F	477	52	51	279	382

were sacrificed moribund or were killed at the final sacrifice constituted the other subset. To keep these two subsets separate, the former will be referred to as the interim sacrifice group and the latter as the nonscheduled sacrifice group. When all the rats in one of the exposed groups had died, the remaining rats in all the other exposed groups were autopsied. This occurred 43 weeks after exposures began and is referred to as the final sacrifice. The number of control rats in each group autopsied at the final sacrifice were equal in number to the rats in each of their respective exposed groups.

At the interim sacrifices, blood was taken from each animal for hematological and clinical chemistry analyses, including measurements for albumin, gamma globulin, alkaline phosphatase, SGOT, SGPT, and γ-glutamyl transpeptidase.

At the autopsies all tissues were examined grossly and sections of liver, kidney, pancreas, spleen, adrenal, thyroid, pituitary, brain, gonads, prostate or uterus, urinary bladder, skin, sternum, paws, lungs, tracheobronchial lymph nodes, mesenteric lymph nodes, salivary gland, zymbal glands and any abnormal tissues from each rat were fixed in neutral buffered 10% formalin, embedded in Paraplast, slide-mounted, stained with hematoxylin and eosin and examined microscopically by a pathologist.

Results

No clinically or statistically significant differences in mean hematological and clinical chemistry measurements were detected between exposed and control groups of the same age and sex at any of the interim sacrifices.

The most frequently occurring tumor types in both sexes of exposed rats were liver angiosarcomas, pituitary adenomas and mammary tumors; in the control groups, pituitary adenomas and mammary tumors. A few rats in both the exposed and control groups were found to have zymbal gland tumors or brain tumors. Although four angiosarcomas occurred in mesenteric lymph nodes and one in the mediastinum in exposed rats, these were not considered to be induced by vinyl chloride since one nonhepatic angiosarcoma (subcutaneous) was also seen in control rats in this experiment and have been seen in control rats in other experiments in a low incidence (< 1%). However, one early angiosarcoma of the spleen and two metastatic angiosarcomas in the lungs (one from a primary in the mesentery) were seen in exposed rats. These were considered to be induced by vinyl chloride and are included in the angiosarcoma statistics.

Since the first liver angiosarcoma did not occur until the 16th week of the study, only those animals alive at that time were considered to be at risk for the development of angiosarcomas. Those are the animals used in the incidence statistics.

A total of 28 out of 370 males and 50 out of 387 females in all exposed groups combined were found to have angiosarcomas. Only one angiosarcoma was seen in all the controls (group 5, male) and it was subcutaneous. The greatest percentage of angiosarcomas were found by far in the nonscheduled sacrifice groups. The exposure times, mean survival times, number of animals at risk, incidence of angiosarcomas and the week that the first angiosarcoma was diagnosed for each age group of males in the nonscheduled sacrifice groups are tabulated (Table 3). Although no angiosarcomas were observed in the two youngest age groups, they were seen in 3/45 (6.7%) of the rats in group 6 and 13/55 (24%) of the rats in group 8. The first angiosarcoma occurred 7 weeks earlier in group 8 than in group 6. Histologically, the angiosarcomas were highly anaplastic and most of them had metastasized.

Similar data concerning the female rats in the nonscheduled sacrifice groups are also tabulated (Table 3). Angiosarcomas were seen in all groups with increasing frequency from group 2 (youngest)

Table 3. Angiosarcomas in exposed male and female rats in nonscheduled sacrifice groups.

Group	Sex	Mean exposure, weeks	Mean survival, weeks	Rats at risk	Angiosarcoma incidence	Incidence of metastases	First appearance of angiosarcomas, weeks
2	M	24.5	30.6	37	0/37	–	–
2	F	24.6	37.5	38	2/38 (5.3%)	2/2	30
4	M	24.4	31.6	44	0/44	–	–
4	F	24.7	33.8	47	7/47 (15%)	5/7	28
6	M	25.0	30.5	45	3/45 (6.7%)	3/3	28
6	F	24.0	30.0	49	23/49 (47%)	10/23	20
8	M	24.5	28.9	55	13/55 (24%)	11/13	21
8	F	23.9	30.2	54	11/54 (20%)	6/11	16

to group 6. The incidence in group 8, however, is lower than in group 6 and closer to that in group 4. The first angiosarcoma, however, was seen in group 8, the oldest group.

In comparing the males and females, it can be seen in Table 3 that the first angiosarcoma appeared earlier in the females in each group and that the incidence was higher in females for each age group, with the exception of group 8, the oldest age category. Since the mean survival times and exposure durations for males and females in groups 4 and 6 were similar, the differences in incidence can be attributed to sex.

The incidences of angiosarcomas in the interim sacrifice, nonscheduled sacrifice and combined groups appear in Table 4. The females sacrificed at 6 and 9 months had a much lower incidence of angiosarcomas than those in the nonscheduled sacrifice groups, whereas, the difference in incidence between similar groups of males was not as great.

The incidences of angiosarcomas in the different age groups were compared using Fisher's exact test. Because of multiple comparisons, the α-level for each individual comparison needed to be ≤ 0.01 for the incidences to be significantly different with an overall $\alpha = 0.05$. In the nonscheduled sacrifice groups, the incidence of angiosarcomas in group 8 males was significantly different from those incidences in group 4 and group 2 males; the incidence of angiosarcomas in group 6 females was significantly different from those in group 4, group 2 and group 8 females. The same comparisons between the same groups in the combined nonscheduled and interim sacrifice groups were also found to be significant.

The effect of age on angiosarcoma incidence in males was examined using the method of weighted least squares regression. A quadratic equation was shown to be a good model for predicting angiosarcoma incidence as a function of age in weeks. The percent of variability in incidence rates (R^2) explained by this model was: $R^2 = 99.96\%$ for nonscheduled sacrifice groups and $R^2 = 99.85\%$ for combined nonscheduled and interim sacrifice groups (Fig. 1). Both of these models were statistically significant ($p = 0.02$ and $p = 0.001$, respectively).

The fact that most of the angiosarcomas in the females occurred in the animals that died spontaneously suggested that their deaths might be directly related to the angiosarcomas. A comparison of mean survival times, however, revealed that animals with angiosarcomas survived as long and frequently longer than other animals in their respective groups (Table 5). At 4-week intervals, the accumulative incidence of angiosarcomas was tabulated (Table 6) for exposed females. Although the incidence of angiosarcomas at all intervals in groups 2 and 6 is about the same, in group 8 the incidence decreases with time, and in group 4 it increases with time.

Although a few brain tumors, mammary adenocarcinomas and zymbal gland tumors occurred in exposed animals, their incidences did not appear to be significantly different from those of the controls.

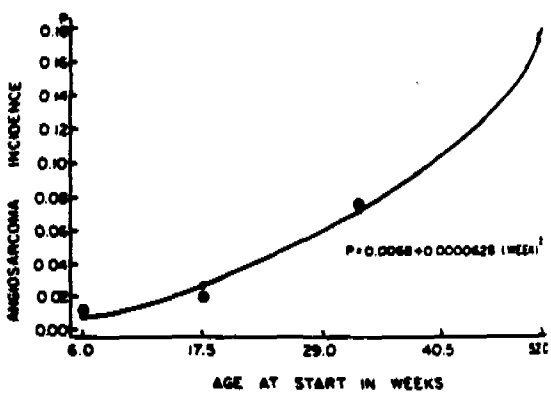

FIGURE 1. Angiosarcoma incidence: males (combined deaths, interim sacrifices and final sacrifice). Curve fitted by regression methods showing a significant quadratic fit. $R^2 = 99.85\%$.

Table 4. Incidence of angiosarcomas in exposed rats, nonscheduled (NS), interim sacrifice (IS) and combined groups.

Group	Sex	NS	IS	Combined NS + IS
2	M	0/87	1/46 (2.2%)	1/83 (1.2%)
2	F	2/38 (5.3%)	0/50	2/88 (2.3%)
4	M	0/44	2/47 (4.3%)	2/91 (2.2%)
4	F	7/47 (15%)	0/50	7/97 (7.2%)
6	M	3/45 (6.7%)	4/49 (8.2%)	7/94 (7.4%)
6	F	23/49 (47%)	4/49 (8.2%)	27/98 (28%)
8	M	13/55 (24%)	5/47 (11%)	18/102 (18%)
8	F	11/54 (20%)	3/50 (6%)	14/104 (13%)

Table 5. Mean survival of exposed rats in nonscheduled sacrifice groups.

	Mean survival, weeks			
	Males		Females	
Group	All rats	Rats with angiosarcomas	All rats	Rats with angiosarcomas
2	30.6	—	37.5	36.5
4	31.6	—	33.8	38.9
6	30.5	35.3	30.0	32.0
8	28.9	31.2	30.2	27.3

Table 6. Accumulative angiosarcoma incidence in exposed females, nonscheduled sacrifice group.

Interval, weeks	Angiosarcoma incidence			
	Group 2	Group 4	Group 6	Group 8
16-19	0/0	0/1	0/2	2/5 (40%)
20-23	0/1	0/5	3/7 (43%)	3/9 (33%)
24-27[a]	0/6	0/14	8/23 (35%)	6/22 (27%)
28-31	1/13 (7.7%)	1/22 (4.5%)	12/31 (39%)	8/34 (24%)
32-35	1/14 (7.1%)	2/28 (7.1%)	14/37 (38%)	10/40 (25%)
36-39	1/15 (6.7%)	3/29 (10%)	18/41 (44%)	11/46 (24%)
40-43	2/38 (5.3%)	7/47 (15%)	23/49 (47%)	11/54 (20%)

[a]Exposures terminated.

Discussion

The results clearly indicate that the incidence of angiosarcomas is higher and these tumors occur earlier in older rats of both sexes. In addition, the incidence of angiosarcomas is generally higher and these tumors occur earlier in female rats than in male rats. Therefore, it can be concluded that older rats are more susceptible to the angiosarcoma-inducing effect of vinyl chloride than are young adult rats and that female rats are more susceptible than males.

The authors have been unable to find comparable studies in the scientific literature. However, Maltoni (*1*) reported in a summary article of his research with vinyl chloride that exposure duration was an important factor in determining angiosarcoma incidence. In that article, he reported that rats exposed to 10,000 ppm vinyl chloride, 4 hr/day, 5 days/week for 17 weeks did not develop liver angiosarcomas within a 155-week period, whereas, 13/60 (22%) of rats exposed to 6,000 ppm vinyl chloride 4 hr/day, 5 days/week for 52 weeks (and held for a 155-week period) developed liver angiosarcomas. In the authors' opinion, the difference in total dose between the two groups was not sufficient to account for the large difference in the angiosarcoma incidences, and that the major factor, therefore, was probably the difference in ages while they were being exposed.

There is suggestive evidence in the literature that older adult humans might be more susceptible than young adults to the carcinogenic effects of Thorotrast. Curry et al. (*2*) stated in their article that "although the latent period between thorium injection and liver malignancy has varied from 3 years to 35 years, all of these 123 cases occurred in patients between 49 and 55 years of age." There is suggestive evidence that older beryllium workers are more susceptible to the carcinogenic effects of beryllium. The data of Mancuso's study (*3*) of beryllium extraction workers show an extremely high risk for lung cancer in workers between the ages of 38 and 65 who were exposed for relatively short periods of time. Studies specifically designed to test this theory in humans, as well as in animals, with other compounds are needed.

If these findings can be reproduced in animals with a wide variety of classes of compounds, then it would be justifiable to modify chronic bioassay experiments by utilizing older animals at the beginning of the studies and shortening the durations of the experiments by 6-12 months. In many cases, this should result in decreasing costs by 20-30% and, thereby, permit a greater number of chemicals to be tested.

The observation in this study that the accumulative incidence of angiosarcomas in the 6-week-old group of rats did not increase with time after discontinuation of the exposures suggests that the carcinogen is metabolized and inhibited or excreted before most of the animals became susceptible. Whether or not these animals would have exhibited a higher incidence of angiosarcoma at some later time is not known. However, as mentioned above, Maltoni (*1*) was unable to induce liver angiosarcomas in young adult rats exposed to 10,000 ppm vinyl chloride 4 hr/day, 5 days/week for 17 weeks and held for a lifetime. The total dose in his experiment was 10,000 ppm × 340 hr (3,400,000 ppm-hr). The total dose in our experiment was 948 ppm × 858 hr (813,384 ppm-hr). Therefore, it is unlikely that the youngest groups in our experiment would have developed a higher incidence of angiosarcomas if they were held for a lifetime.

The results of this study also suggest that older people should not be preferentially placed in carcinogenic working environments.

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Discussion

In this animal model, ingested ethanol is a cocarcinogen in relation to VC induction of tumors in the liver. The incidence of angiosarcoma in VC-ethanol dosed rats (50%) was more than double that resulting from VC exposure alone (23%). VC-ethanol also induced a greater number of hepatocellular carcinomas (60%) than occurred in VC-treated animals (44%). The first deaths from angiosarcoma and carcinoma of the liver occurred earlier in VC-ethanol dosed animals indicating a shortened latent period.

The Sprague-Dawley rats used by Maltoni and Lefemine in 1974 (*4*) were more resistant to the effects of VC on the liver than the animals used in this VC-ethanol study. Following a year-long exposure to 500 ppm VC 4 hr/day, 5 days/week and observation from first VC exposure for 135 weeks, only 7 of 59 rats (12%) were reported to have angiosarcoma in the liver (*4*). Angiosarcomas developed in other sites such as in subcutaneous tissue, the abdominal cavity, neck, lung and uterus. Hepatocellular carcinomas were not reported. Zymbal gland carcinomas were seen in 8% of Maltoni's VC exposed animals; none were seen in this study.

Ethanol has been reported to potentiate the toxicity of other halogenated hydrocarbons. In whole animals, a variety of alcohols increased the hepatotoxicity of carbon tetrachloride (CCl_4) when ingested 16 to 18 hr prior to inhalation of CCl_4 (*7*). Following acute exposures, CCl_4 toxicity was enhanced by ethanol as judged by the elevation of serum glutamic-oxaloacetic transaminase levels. In similar studies, trichloroethylene (TCE) or 1,1,1-trichloroethane hepatotoxicity was potentiated by ethanol, but only at high concentrations of inhaled TCE or 1,1,1-trichloroethane (*8*).

Ethanol potentiation of VC carcinogenesis in the liver is probably due to an effect on VC metabolism. Inhibition of VC uptake (*5*) and metabolism (*6*) by ethanol suggests there is a shared step in the oxidation of the two toxic agents. The most like candidates for competition are acetaldehyde a chloroacetaldehyde. The normal substrate, acet dehyde, would be oxidized preferentially result in an increased half-life of chloroacetaldehyde.

Toxic manifestations of exposures were fou which were not related to the neoplastic respons Many animals died because of neoplasms or secon ary changes caused by tumors; however, dea directly attributable to toxicity was not seen. T toxicity of ethanol will be discussed in anothe publication.

I wish to thank Frank Grande, Morris Blackstone and Jan Kurzhals for their technical assistance and Dianne Dotson secretarial support.

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Cancer Induction Following Single and Multiple Exposures to a Constant Amount of Vinyl Chloride Monomer

by Robert M. Hehir,* Bernard P. McNamara,†** Joseph McLaughlin, Jr.,* Donald A. Willigan,‡ George Bierbower* and Jerry F. Hardisty†

Vinyl chloride monomer (VCM), already identified as a human animal carcinogen, was selected as a model agent to explore an area of concern for single and intermittent low level exposure. In traditional cancer bioassay, animals are repeatedly exposed over their lifespan to a dose of suspected chemical.

In the current studies rats and mice were exposed in an inhalation chamber to single one-hour doses of VCM ranging from 50 to 50,000 ppm.

A second group was given 10 one-hour exposures to 500 ppm or 100 one-hour exposures to 50 ppm of the same chemical. All animals were then observed for the remainder of their lives, generally 18-24 months. Moribund animals were euthanized, and survivors were sacrificed on schedule and their tissues examined for pathological changes. Specifically, the oncogenic study demonstrated dose related effects for single one-hour exposure of VCM at high levels, i.e., 5,000 and 50,000 ppm. These concentrations increased the incidence of pulmonary adenomas and carcinomas in mice.

Repeated exposure of A/J mice to the same chemical at 500 ppm × 10 one-hour exposures also increased the incidence of pulmonary adenomas and carcinomas which are considered highly significant ($p = 0.001$) when compared to match controls. At the lower dose of 50 ppm × 100 one-hour exposure, no significant increase in tumors was observed. Rats exposed to identical concentrations of VCM failed to elicit a tumorigenic response.

Introduction

In the last decade there have been concerted efforts by industry and the Federal government to identify carcinogenic substances in the workplace. However, carcinogens are not limited to occupational exposures. Many of these same chemicals are also used in the formulation of household products. Therefore, consumers in all walks of life may be exposed to suspect chemicals in their homes without their knowledge. This type of consumer exposure is usually brief and at very low levels. The suspect chemical may be modified in the process of manufacturing the consumer product, i.e., as in the case of polymerization of vinyl chloride (VC) to poly(vinyl chloride) (PVC), or trace quantities of the unreacted monomer may be present in the product which may be leached out under normal conditions of use. There are other situations wherein a chemical like VC is used because it is chemically inert, for example as a propellant, and as an unreacted gaseous chemical it could become a potential health problem.

While regulatory bodies try to establish safe exposure levels and industry attempts to control exposures in the production facilities, no such control measures would be of practical value in the

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home environment. Another complication associated with making value judgements about potential risks of consumer exposure is that traditional cancer bioassays involve daily exposures to the test chemical over the animal's lifetime. There were no comparable studies on short-term exposure to a carcinogen like VC followed by a lifetime monitoring for toxicological symptoms with complete histopathological examination at death. Therefore, our approach was to explore what happens to laboratory animals following brief or intermittent exposure to a known carcinogen like VC. Vinyl chloride appeared to be the ideal chemical to use in these experiments because of its widespread use in industrial and consumer products. Furthermore, the relationship for inducing unique pathological lesions, i.e., angiosarcoma of the liver for high exposure levels in animal and man was already established by Viola et al. (*1*) Maltoni (*2*) and Creech et al. (*3*).

Quite apart from the need to establish a bench mark for acute short-term intermittent exposures to a carcinogen, such as vinyl chloride, was the question of "threshold effects" or "safety factor" for low level exposures. In setting up our experiments we were mindful of the many factors that could have an impact on the study design. Some of the more important factors are that (1) the substance may not reach a susceptible cell; (2) the substance may make noncarcinogenic biochemical combination with the cell; (3) the "initiated" lesion may not receive adequate "promotion"; (4) host factors may be unfavorable to carcinogenesis; (5) biochemical repair of the DNA lesion may occur; (6) morphological regression of tumorigenic proliferation may occur; (7) carcinogenic cells may be destroyed by the body's immune system. These items need to be addressed in any conventional cancer bioassay but are even more critical in searching for noncarcinogenic exposure levels.

Experimental Conditions

Two strains of rats, Fischer 344 (Charles River Laboratory, Wilmington, Mass.) and Sprague-Dawley/Wistar (Chemical Systems Lab, Edgewood, Md.), and two strains of mice, A/J (Jackson Lab, Bar Harbor, Maine) and ICR (Charles River Laboratory) were treated in single or multiple intermittent inhalation exposures to VC. The chambers were Rochester type, stainless steel, 1000 liter, constructed to provide laminar air flow and insure uniform exposures to VC to test animals.

Chamber concentrations were established by proportioning the amounts of VC being dispersed with the air flow through the chamber. Airflow through the chamber was created by a blower motor located in the flow pipe on the exhaust side of the chamber. A negative pressure was maintained in the chamber at all times when operational and the exhaust gas completely filtered (M6A1 gas-particulate filter) before discharge to the environment. The concentration of gas in the inhalation chamber was monitored by using a Hewlett-Packard 5830A gas chromatograph with a dual flame ionization detector.

Exposure Procedures for VC Lifetime Cancer Studies

Male and female rats and Fischer 344 and ICR mice were totally exposed for 1 hr to 50, 500, 5000 and 50,000 ppm VC. Fischer rats and A/J mice equally divided by sex received ten 1 hr exposures to 500 ppm VC (1 hr/day, 5 days/wk for 2 weeks) or 100 1-hr exposures to 50 ppm (1 hr/day, 5 days/wk for 20 weeks). Male and female parents (Sprague-Dawley/Wistar) rats (obtained from Veterinary Medical Division, Edgewood Arsenal, Md.) from the reproduction study were also maintained and observed for 24 months post exposure to 50 to 500 ppm VC 1 hr per day, 5 days per week for 10 weeks (49 exposures).

Following exposure, all animals were air washed until the chamber concentration was less than 1 ppm VC. Animals of the same sex were segregated in stainless steel cages with a maximum number of 5 rats in each compartment and placed in the animal holding area. Mice were similarly treated, but smaller cages were used and the number of mice per compartment was limited to two. The animals were observed twice daily for general health, sores, masses, alertness, activity or mortality. All animals were weighed weekly for the first 8 weeks post exposure and monthly thereafter. The exposure schedules for the studies described above are shown in Tables 1-3. No blood chemistries or hematology studies were performed.

Pathology

Gross and Light Microscopy. A complete gross and microscropic examination was performed on most control and exposed animals which died or were sacrificed. Autolysis precluded such examination in a few cases.

All rodents were to be serially sacrificed at 8, 16 and 24 months post exposure. However, the life span of the mice forced some changes in the later times of sacrifice and termination of mouse experiments. For single exposure the planned 16 and 24 month sacrifice were replaced by 18 month sacrifices.

Table 1. Single exposure schedule of animals to VC.

Species	Sex	Dose, ppm	Exposure date AM	Exposure date PM	Exposure group size	Age at time of exposure, weeks
Fischer 344 rat	M	50	3/4/75		90	15
		500	3/11/75		90	16
		5000	3/18/75		85	17
		50000	3/25/75		90	18
	F	50		3/4/75	90	15
		500		3/11/75	100	16
		5000		3/18/75	95	17
		50000		3/25/75	88	18
ICR mouse	M	50	3/4/75		90	15
		500	3/11/75		90	16
		5000	3/18/75		90	17
		50000	3/25/75		90	18
	F	50		3/4/75	90	15
		500		3/11/75	90	16
		5000		3/18/75	90	17
		50000		3/25/75	90	18
Rat	M	Neg/Cont.			92	15–18
	F	Neg/Cont.			79	15–18
Mouse	M	Neg/Cont.			82	15–18
	F	Neg/Cont.			88	15–18

Table 2. Exposure schedule for animals exposed repeatedly to VC.

Species	Sex	Dose, ppm	Exposure periods, days	Exposure dates From	Exposure dates To	Exposure group size Start	Exposure group size End	Age, weeks Start	Age, weeks End
Fischer rat	M	50	100	8/27/75	1/26/76	90	86	21	41
		500	10	7/1/75	7/28/75	90	90	14	16
	F	50	100	8/27/75	1/26/76	90	87	21	41
		500	10	7/1/75	7/18/75	90	90	14	16
A/J mouse	M	50	100	7/1/75	7/18/75	90	87	15	35
		500	10	8/27/75	1/26/76	90	90	8	10
	F	50	100	7/1/75	7/18/75	90	88	15	35
		500	10	8/27/75	1/26/76	90	90	8	10
Fischer rat	M	Neg.	100(c)[a]	—		50	50	21	41
		Control	10(c)	—		50	50	14	16
	F	Neg.	100(c)	—		50	47	21	41
		Control	10(c)	—		50	50	14	16
A/J mouse	M	Neg.	100(c)	—		40	39	15	35
		Control	10(c)	—		50	50	8	10
	F	Neg.	100(c)			50	50	15	35
		Control	10(c)	—		50	50	8	10

[a](c) denotes control for corresponding dose above.

Table 3. VC multigeneration study, F_0 parents.[a]

Group	Compound	Dose[b]	Number of males	Number of females
I	Air	Control	25	25
II	VC	Low dose (50 ppm)	25	25
III	VC	High dose (500 ppm)	25	25

[a]Sprague-Dawley/Wistar rats.
[b]Exposure to 50 or 500 PPM of VC 1 hr/day, 5 days/week for 10 weeks (49 exposures) before mating.

This observation period was the minimum suggested by the National Cancer Institute (4) for cancer bioassays in small animals. For multiple dose studies in mice the final sacrifice was at 20 months rather than 24 months. The change was made in consideration of the risk of animal loss through death and possible cannibalism. Tissues examined were lung, trachea, heart, liver, stomach, small intestines, spleen, kidney, bladder, bone marrow (sternum), adrenals, pancreas, duodenum, brain, eye, zymbal gland, ear, nose, muscle and bone (femur).

Electron Microscopic Studies. Groups of five male and five female Fisher (344) rats from each of the single 1-hr exposure studies (50, 500, 5000 and 50,000 ppm) with equal numbers of their corresponding control groups were sacrificed at 8, 16, 24 months.

Groups of five male and five female Fischer (344) rats from the multiple 1-hr exposure studies at 50 and 500 ppm VC along with equal numbers of control animals were sacrificed at 16 and 24 months.

Results

Toxicity During Exposure

Rats and mice exposed for 1 hr to concentrations of VC ranging from 50 to 50,000 ppm or for repeated exposures, i.e., 50 ppm or 500 ppm, produced no remarkable signs of toxicity with the exception of mice at the 50,000 ppm level. At 50,000 ppm VC 50% of the male mice exhibited hyperventilation at 45 minutes together with twitching and possible ataxia. Female mice became hyperactive after 40 min exposure, and respiratory difficulty and ataxia was observed in approximately 25% of the female mice after 55 min. Upon removal from the test atmosphere, all animals recovered to normal appearance within 24 hr. After exposure there were no consistent or dose-related differences between control and exposed (single or multiple) mice or rats in death rate, toxic signs or change in body weight.

Gross Pathology

There was a suggestion of higher frequency of masses in the lungs and livers of mice exposed once or repeatedly to VC at the higher dose levels, i.e. 500, 5000 or 50,000 ppm.

Histological Examination of ICR Mice: Single Exposure

Changes ascribable to vinyl chloride were apparent primarily in the lungs with the induction of pulmonary adenomas and pneumonitis. Pneumonitis was evident in all animal groups which were exposed to VC at 500 ppm and above.

The development of bronchio-alveolar adenomas increased with exposure to higher dose levels of VC. Tables 4 and 5 summarize the significant histological changes observed in ICR mice at 8 and 16 months following single exposure to graded doses of VC.

Mice were more susceptible than rats to pneumonitis following exposure to VC. The effect however was not incremental with dose level. The incidence of pneumonitis, adenoma and carcinoma in ICR mice following single exposure is presented in Table 6. No correlation was observed between the incidence of pneumonitis and adenoma or pneumonitis and carcinoma. However, males seemed more prone to the induction of pneumonitis, particularly at 50,000 ppm, i.e., 34% M vs. 13% F. At 5000 ppm and below, male and females were about equally sensitive.

There was an increase in bronchio-alveolar adenomas with exposure to higher doses of VC and the condition manifests itself more frequently in males, i.e., at 50,000 ppm: 51% M vs. 18% F. This trend continued at the 5000 ppm: 22% M vs. 13% F. Males and females were equally susceptible at dose level 500 ppm and below. The upper respiratory tract (nasal turbinates) and trachea revealed no unusual changes specifically attributable to VC.

Table 4. Histological examination of ICR mice at 8 and 18 months following a single (1-hr) exposure to vinyl chloride monomer.

Vinyl chloride concentration, ppm	Histological changes attributable to vinyl chloride	
	Induction of pulmonary adenomas	Progression to carcinoma
50,000[a]	45/137 (33.8%)	3/137 (2.2%)
5,000[a]	24/143 (16.8%)	1/143 (0.7%)
500[a]	18/139 (12.9%)	1/139 (0.7%)
50	14/139 (10.1%)	0/139 (0%)
0 (control)	12/120 (10.0%)	0/120 (0%)

[a]Pneumonitis was evident in all animal groups which were exposed to VCM at doses of 500 ppm or more.

Histological Examination of A/J Mice at 8, 16 and 20 Months Following Multiple Exposure

500 ppm, 10 days, 1 hr. Changes ascribable to VC were apparent in the lung only, primarily the induction of pulmonary adenomas. Bronchio-alveolar adenomas were induced in the test group with approximately equal frequency in males and females, i.e., 73.7% M vs. 75.6% F, respectively. The increase in incidence as shown in Table 7 for the test group over that of the controls was substantial, by a factor of 2.2, i.e., controls, 34.4%; 500 ppm; 74.7.

Progression to malignancy (carcinoma) in the test group vs. controls was also highly significant: controls, 3/90 or 3.3%; 500 ppm, 22/166 or 13.3%. In animals scheduled for evaluation (survivors) pulmonary adenomas were observed as early as 8 months post exposure in 60% of males and females; at 20 months, 75% of animals were affected.

The incidence of pneumonitis, adenoma and carcinoma in A/J mice following multiple exposure to VC is presented in Table 8. Pneumonitis was observed more frequently in the control animal than

Table 5. Overall summary: incidence of nonneoplastic changes and histologically proven neoplasms within the liver and lungs of ICR Swiss mice exposed to vinyl chloride in single inhalation exposures.

	Incidence of response for various vinyl chloride concns									
	0		50,000 ppm		5,000 ppm		500 ppm		50 ppm	
Tissue response	M (62)[a]	F (77)[a]	M (74)[a]	F (82)[a]	M (76)[a]	F (82)[a]	M (72)[a]	F (75)[a]	M (81)[a]	F (80)[a]
Liver (number evaluated)	50	75	68	78	68	76	67	72	64	68
Hepatic cell necrosis	2	10	3	5	6	7	4	6	2	3
Hepatic cell vacuolation (lipidosis)	2	11		4	2	12	3	5	1	4
Hepatic cell hypertrophy	1		2	8		8	4	18	1	
Hepatic cell hyperplasia					4	4				
Angiectasis				1		4				
Sinusoidal reticulosis				5						
Hepatic cell adenoma	2		1			1			2	
Hepatic cell carcinoma	2		4	1	6	1	9		2	
Hemangioma					1					
Hemangiosarcoma	1									
Lung (number evaluated)	50	70	61	76	65	78	66	73	71	68
Pneumonitis	1	6	21	10	13	17	19	15	4	7
Bronchio-alveolar adenoma	4	8	31	14	14	10	8	10	8	6
Bronchio-alveolar carcinoma			1	2	1			1		

[a]Numbers in parentheses denote animals per group. Total includes animals from scheduled sacrificed (8 and month periods) and spontaneous deaths.

Table 6. Single inhalation exposure of ICR mice to vinyl chloride monomer.

VC exposure concn, ppm	Group	Lung tissue: incidence of response/number evaluated[a]		
		Pneumonitis	Adenoma	Carcinoma
0 (control)	Male	1/50 (2%)	4/50 (8%)	0/50 (0%)
	Female	6/70 (9%)	8/70 (11%)	0/70 (0%)
	Combined (M + F)	7/120 (6%)	12/120 (10%)	0/120 (0%)
50,000	Male	21/61 (34%)	31/61 (51%)	1/61 (2%)
	Female	10/76 (13%)	14/76 (18%)	2/76 (3%)
	Combined (M + F)	31/137 (23%)	45/137 (33%)	3/137 (2%)
5,000	Male	13/65 (25%)	14/65 (22%)	1/65 (2%)
	Female	17/78 (22%)	10/78 (13%)	0/78 (0%)
	Combined (M + F)	30/143 (21%)	24/143 (17%)	1/143 (1%)
500	Male	19/66 (29%)	8/66 (12%)	0/66 (0%)
	Female	15/73 (21%)	10/73 (14%)	1/73 (1%)
	Combined (M + F)	34/139 (24%)	18/139 (13%)	1/139 (1%)
50	Male	4/71 (6%)	8/71 (11%)	0/71 (0%)
	Female	7/68 (10%)	6/68 (9%)	0/68 (0%)
	Combined (M + F)	11/139 (8%)	14/139 (10%)	0/139 (0%)

[a]Total includes animals from scheduled sacrifice (8, 16, 20 months period) and spontaneous deaths.

in either test group. No correlation was observed between the incidence of pneumonitis and adenoma or for pneumonitis and carcinoma. These results are similar to those observed in the single exposure study.

50 ppm, 100 days, 1 hr. Again changes attributable to VC were apparent in the lung only, primarily pulmonary adenomas. However, the incidence in the induction of adenomas and progression to carcinoma are considered only marginal and not statistically significant.

Comparatively, the potential for development of pulmonary adenomas as shown in Table 7 was greater in A/J mice following multiple exposures at 500 ppm than at 50 ppm, i.e., incidence at 500 ppm, 74.7%; at 50 ppm, 44.1%, despite an equivalent total dose of 5000 ppm VC. Also, pulmonary adenomas were induced earliest (8 months) following multiple exposures at 500 ppm. It is also of interest that the control groups of A/J mice for both multiple inhala... studies showed a baseline incidence for pulmo... adenomas which was nearly identical, i.e., at ... ppm, 34.4%; at 50 ppm, 34.5%.

Table 9 provides an overall summary of the in... dence of histologically proven neoplasms obser... in both strains of mice, i.e., ICR and A/J, follow... single and multiple exposures to VC. The neopl... tic and nonneoplastic changes observed in the li... and/or lungs of A/J mice following multiple ex... sures to VC at 50 and 500 ppm are shown in Tab... 10 and 11. Although other neoplasms and nonn... plastic changes occurred variously in all remain... organs and tissues, the response appeared eith... sporadically or was shared by all test groups incl... ing controls. Relationship by incidence and severi... to test exposure was not evident. Furthermo... morphologic deviations were not unlike those no... mally observed in aging A/J mice maintained und... standard laboratory conditions.

Table 7. Histological examination of A/J mice at 8, 16 and 20 months following multiple (1-hr) exposures to vinyl chloride monomer.

Number of exposures and concentration of VCM	Histological changes attributable to vinyl chloride monomer	
	Induction of pulmonary adenomas	Progression to carcinoma
0 (controls)	31/90 (34.4%)	3/90 (3.3%)
10 × 500 ppm[a]	124/166 (74.7%)	22/166 (13.3%)
0 (controls)	29/84 (34.5%)	2/84 (2.4%)
100 × 50 ppm[b]	65/158 (44.1%)	7/158 (4.4%)

[a]Highly significant difference in the number of pulmonary adenomas ($p = 0.001$) observed at the 500 ppm × 10 hr exposure level versus control by Z test.

[b]No significant difference for pulmonary adenomas ($p < 0.14$) and carcinomas ($p = 0.19$) observed at the lower multiple exposure level.

Electron Microscopic Results

In general, these studies indicate that expos... to vinyl chloride increased organelle turnover as w... as loss of volume control (bleb formation) and i... creased lysosomal activity in the liver of rats. The... alterations progressively decreased as recovery af... exposure increased.

Hepatocellular carcinoma was seen in one ma... Fischer rat which had received 10 exposures of 5... ppm. Lymphosarcoma was noted in one fema... Fischer rat which had received a single exposure a... 500 ppm. Since these were individual cases an... since no cancers were seen at 50,000 ppm, th... lymphosarcoma and the hepatocellular carcino... are not likely related to vinyl chloride exposure.

Table 8. Multiple inhalation exposure of A/J mice to vinyl chloride monomer.

VC Exposure			Lung tissue: incidence of response/number evaluated[a]		
Frequency	conen, ppm	Group	Pneumonitis	Adenoma	Carcinoma
10 × 1	0	Male	0/43 (0%)	15/43 (35%)	0/43 (0%)
		Female	2/47 (4%)	16/47 (34%)	3/47 (6%)
		Combined (M + F)	2/90 (2%)	31/90 (34%)	3/90 (3%)
10 × 1	500	Male	0/76 (0%)	56/76 (74%)	12/76 (16%)
		Female	0/90 (0%)	68/90 (76%)	10/90 (11%)
		Combined (M + F)	0/166 (0%)	124/166 (75%)	22/166 (13%)
100 × 1	0	Male	5/39 (13%)	11/39 (29%)	2/39 (5%)
		Female	3/45 (7%)	18/45 (40%)	0/45 (0%)
		Combined (M + F)	8/84 (10%)	29/84 (35%)	2/84 (2%)
100 × 1	50	Male	4/77 (5%)	27/77 (35%)	3/77 (4%)
		Female	5/81 (6%)	38/81 (47%)	4/81 (5%)
		Combined (M + F)	9/158 (6%)	65/158 (41%)	7/158 (4%)

[a]Total includes animals from scheduled sacrifice (8, 16, 20 months period) and spontaneous deaths.

Reproduction Carcinogenesis Study

One hundred and fifty colony rats (Sprague-Dawley/Wistar) were divided into three groups of equal numbers of males and females. These specific-pathogen-free, random bred animals were obtained from the Animal Resources Branch at Edgewood Arsenal. The rats were 12 weeks old when initially exposed to VC. One hundred rats were exposed as described and the remaining 50 were carried as unexposed controls. The parental generations of S-D W rats were maintained 24 months post exposure for carcinogenic evaluation.

A complete gross and microscopic pathological examination of all tissues was performed on each control and exposed animal. Particular emphasis was placed on examination of brain, lung, and liver tissues and zymbal gland in the rodent ear. The livers of randomly selected rats were prepared and examined by electron microscopic techniques.

Neoplastic and nonneoplastic lesions were observed in approximately equal frequency in control and F_0 parent generation of Sprague-Dawley/Wistar rats exposed to 50 ppm or 500 ppm of VC, 1 hr per day, five days per week for 10 weeks (49 exposures).

The only lesions that occurred in higher frequency in the exposed animals than in control rats were eosinophilic cellular alterations presented as foci/ or areas. The appearance of these foci was related to the dosage of VC. The nature of these lesions are of interest but as yet are controversial, so that no inference can be drawn.

Table 9. Summary of incidence of histologically proven neoplasms observed within tissues of mice at various intervals following single or multiple exposures to vinyl chloride monomer.

Inhalation exposure	Exposure concentration, ppm	Number of neoplasms observed (scheduled sacrifice) 8 months	16 months	18 months	20 months	Totals	Total number of neoplasms observed
Single (1 hr)	50,000	5		24		29	110
	5,000	3		18		21	78
	500	1		29		30	82
	50	0		16		16	62
	0 (control)	0		14		14	72
Multiple (1 hr)	500 × 10	12	22		70	104	170
	0 (control)	0	2		38	40	45
	50 × 100	4	16		63	83	137
	0 (control)	1	5		27	33	41

[a]ICR strain used in single (1 hr) exposure studies; and A/J mice used in the multiple (1 hr) exposure studies.

Table 10. Overall summary: incidence of nonneoplastic changes and histologically proven neoplasms within the lungs of A/J mice exposed to vinyl chloride in multiple inhalation exposures.

Tissue response	Incidence of response: Control (0 ppm), 100 × 1 M (39)[a]	F (47)[a]	Vinyl chloride, 50 ppm, 100 × 1 M (81)[a]	F (83)[a]
Lung (number evaluated)	39	45	77	81
Edema	2			
Congestion	4	1	1	
Focal hemorrhage	2		2	
Pneumonitis	5	3	4	5
Bronchio-alveolar hyperplasia		3		3
Osseous metaplasia				1
Bronchio-alveolar adenoma	11	18	27	38
Bronchio-alveolar carcinoma	2		3	4
Reticulum cell sarcoma				1
	13	18	30	43

[a]Numbers in parentheses denote animals per group. Total includes animals from scheduled sacrifice (8, 16, 20 month periods) and spontaneous deaths.

Discussion

The fact that the severity of carcinogenic effects of VC had been described by various investigators like Maltoni (*2,5*) and Lee et al. (*6*) to coincide with dose and length of exposure implies that the total dosage (concentration × exposure time) may be an important factor in the carcinogenicity of VC. Therefore, the inhaled dose was approximated by the Haber (*7*) concept. In its simplest form this concept states that the dosage, Ct is the product of C (concentration in milligrams/cubic meters) and t (time in minutes). The total concentration can also be expressed in parts per million (ppm) and the time can be expressed in hours, producing Ct ppm-hr. Factors for breathing rate and detoxication can be added. However, this simplified approximation of total inhaled dose is relatively useful, as is, for comparative purposes.

In his experiments Maltoni (*5, 10*) exposed rats and mice as shown in Table 12 to a series of doses of VC ranging from 50 to 10,000 ppm for 4 hr/day, 5 days per week for 52 weeks. The results indicate a questionable carcinogenic effect at 50 ppm or total dosage of 52,000 ppm-hr after 135 weeks. In another experiment (BT3), Sprague-Dawley rats, treated in a similar fashion to BT1 but for 17 weeks only, show after 86 weeks a negative carcinogenic re-

Table 11. Overall summary: incidence of nonneoplastic changes and histologically proven neoplasms within the liver and lung of A/J mice exposed to vinyl chloride in multiple inhalation exposures.

	Incidence of response			
	Control (0 ppm), 10 × 1		Vinyl chloride, 500 ppm, 10 × 1	
Tissue/response	M (46)[a]	F (48)[a]	M (78)[a]	F (92)[a]
Liver (number evaluated)[a,b]	45	48	78	89
Hepatic cell necrosis	4	6	6	13
Lymphoid cell infiltrate	1		1	
Hepatic cell lipidosis	2		2	
Neutrophil infiltrate	2			1
Bile duct hyperplasia	1			
Granulomatous foci			1	
Sinusoidal reticulosis				1
Hepatocyst				1
Amyloidosis			1	
Angiectasis				1
Hepatic cell adenoma	1			
Cholangiocarcinoma	—	—	1	—
	11	6	13	16
Lung (number evaluated)	48	47	76	90
Edema				1
Pneumonitis		2		
Bronchio-alveolar hyperplasia	2	1		2
Bronchio-alveolar adenoma	15	16	56	68
Bronchio-alveolar carcinoma	—	3	12	10
	17	22	68	81

[a]Numbers in parentheses denote animals per group. Total includes animals from scheduled sacrifice (8, 16, 20 month periods) and spontaneous deaths.

Table 12. Maltoni vinyl chloride studies.[a]

Test	Species	Results (carcinogenesis), ppm-hr
BT1	RATS	Questionable at 52,000
BT3	RATS	Negative at 17,000 Questionable at 85,000 Positive at 170,000; 850,000; 2,000,000; 3,000,000
BT6	RATS	Positive at 24,600,000
BT7	RATS	Negative at 52,000 and 260,000 Questionable at 520,000 Positive at 2,600,000; 6,200,000; 10,400,000
BT4	MICE	Positive at 30,000; 150,000; 300,000; 600,000; 1,500,000; 3,600,000

sponse at a total dose of 17,000 ppm-hr, a questionable response at 85,000 ppm and a positive carcinogenic response at 170,000 ppm-hr and above. In experiment BT7, Wistar rats treated with VC at doses ranging from 50 to 10,000 ppm, for 4 hr daily, 5 days/week for 52 weeks in the same manner as described above show positive carcinogenic affects at total dosage of 2,600,000 ppm-hr. The author suggests from comparison of the experimental data obtained with two different strains of rats (BT1/BT3), Sprague-Dawley and (BT7) Wistar, that the strain seems to be a factor in neoplastic response. Based upon neoplastic lesions observed, the Wistar strain was less responsive than Sprague-Dawley. Experiment BT4 with Swiss mice, involving exposure to VC at 50 to 10,000 ppm, 4 hr per day, 5 days per week for 30 weeks produced carcinogenic effects with a total dosage *Ct* of 30,000 to 3,600,000 ppm-hr.

In the studies of Viola, Bigotti and Caputo (*1*), tumors were seen in rats which had been exposed to 30,000 ppm VC, 4 hr/day, 5 days/week, for 12 months. The total dose (*Ct*) of VC was 28,800,000 ppm-hr.

In the studies of Caputo, Viola and Bigotti (*8*), rats and rabbits were exposed to VC for 4 hr/day, 5 days/week for 12 months at six dose levels. The exposure to 50 ppm VC or total dose of 48,000 ppm-hr produced no tumors. Carcinogenic effects were observed at total dosage of 320,000 ppm-hr and above for rats and at 7,800,000 ppm-hr for rabbits.

Keplinger et al. (*9*) exposed rats, hamsters and mice to VC. Only the data on mice were sufficiently complete for examination of total dose effect. Total dosage of 56,000 ppm-hr and above produced tumors in mice. The final report on the rats and hamsters is still unavailable for evaluation.

Lee et al. (*6*) exposed mice and rats to three levels of VC: 50, 250 and 1000 ppm, 5 hr/day, 5 days/week for up to 12 months. All tests with a total dose of 48,000 ppm-hr and below were essentially negative for mice. Positive carcinogenic effects were noted, however, in mice above 78,000 ppm-hr.

The results of our study indicate that a positive carcinogenic effect in rats may not appear until the total dose (*Ct*) of VC exceeds 50,000 ppm-hr. The single exposure study with ICR mice was negative at 50 and 500 ppm-hr, borderline at 5000 ppm-hr but did produce neoplastic lesions in the lung at 50,000 ppm-hr. The A/J mice exposed to multiple doses of VC, i.e., 50 ppm × 100 days × 1 hr or 500 ppm × 10 days × 1 hr for a total cumulative dose of VC of 5000 ppm-hr show a significant tumorigenic response, but only at the higher dose level.

In our studies Fischer rats exposed to a total dosage of 50, 500, 5000, and 50,000 ppm VC for 1 hr showed no chemically induced tumor response. Neither did the Sprague-Dawley/Wistar rats that were exposed to 500 ppm VC 1 hr/ day, 5 days/week for 10 weeks (total dosage 24,500 ppm-hr).

Table 13 summarizes various investigators' test results, including our own, on vinyl chloride. The tests with ICR mice, single exposure to VC, show an increased frequency of adenomas at total dosage of 5000 ppm-hr and above. For A/J mice, repeated exposures to 50 and 500 ppm VC for a total dosage of 5000 ppm-hr shows a similar dose response pattern for adenomas. In general, in terms of total dosage *Ct*, carcinogenic effects are seen in the two mice strains at *Ct* levels of 5000 to 50,000 ppm-hr. Thus total dosage for carcinogenicity in mice is in general agreement with Lee et al. (*6*) (78,000 ppm-hr) and Maltoni (*5*) (between 30,000 and 150,000 ppm-hr) and other investigators.

There is no doubt that risk is related to length of exposure and hence total dose. In our discussion much attention has been focused on the risk of cancer associated with total dosage of VC. However, the multiple exposure experiment at 50 and 500 ppm dose levels with A/J mice for an equivalent total exposure to 5000 ppm-hr appears inconsistent with the thesis of total dosage. Indeed, it appears

Table 13. Other vinyl chloride studies.

Authors	Species	Results (carcinogenesis), ppm-hr
Viola, Bigotti and Caputo (*1*)	Rats	Positive 28,800,000
Caputo, Viola and Bigotti (*8*)	Rats	Negative at 48,000 Positive at 320,000; 1,280,000; 3,200,000; 6,400,000; 12,800,000
	Rabbits	Positive at 7,200,000
Keplinger et al. (*9*)	Mice (rats and hamsters)	Positive at 56,000
Lee (*6*)	Mice	All tests essentially negative below 78,000 and positive above 78,000
Consumer Product Safety Commission (1979)	ICR mice	50 and 500, negative 5000, borderline positive
	A/J mice	50,000 positive
	Fischer rats	50, 500, 5000 and 50,000, negative 24,500, eosinophilic loci, no cancers

from our own data that concentration may be the dominant factor for acute or low level intermittent exposures. This result may be explained on the basis of a number of factors, i.e., metabolism, detoxication, DNA repair or a time for tumor development for low level exposure beyond the animals' lifespan.

As is evident from Table 13, the two strains of rats, Fischer (344) and S-D/W, were more resistant to the adverse effects of single and multiple intermittent exposures of VC.

Our studies are in agreement as to the dose-time relationship for carcinogenesis related to the VC exposure. All of the continuous exposure studies considered collectively indicate that there is a lifetime total dose (Ct) for VC. However, from our own studies with single or intermittent low level exposures to VC we believe that concentration may be the most dominant factor in whether or not carcinogenic effects are observed. For single dose studies with VC in ICR mice, neoplastic lesions were produced at 5000 ppm. For multiple intermittent exposures studies with A/J mice the critical concentration for VC was 500 ppm, total dosage 5000 ppm-hr.

Approximate carcinogenic Ct levels of VC based on data for mice and rats are Ct = 5,000–50,000 ppm-hr, carcinogenic tendencies; 500,000 Ct > 50,000 ppm-hr, definite carcinogenicity; Ct > 500,000 ppm-hr, high incidence of carcinogenicity.

Considerations of Carcinogenicity of VC: Conclusions

Cancer seems dependent on total dose of vinyl chloride, especially in life-time exposure studies, but for short-term exposure the concentration may be the most critical factor.

One dose is sufficient if dose is high enough. The carcinogenic total dose was 5000 ppm-hr for mice and 50,000 ppm-hr for rats.

There were apparent noncarcinogenic doses in the study.

Mice were more sensitive indicators than rats for carcinogenic effects of vinyl chloride.

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Pneumoconiosis in Animals Exposed to Poly(vinyl Chloride) Dust

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Rats, guinea pigs and monkeys were exposed by inhalation (6 hr/day, 5 days/week) for up to 22 months to a 13 mg/m³ 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 poly(vinyl 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 (*1–6*). 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, fiberboard 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 3000

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lb/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/min with a negative chamber pressure of 0.2 in. water. Animals were exposed to PVC dust 6 hr/day, 5 days/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/min for 20 min, through DM 5 μm pore size Metricel filters with a vacuum pump. In addition, simultaneous samples consisting of particles with an aerodynamic diameter ≥ 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 6-hr 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 and that of the exposed group 3361 g. In the ensuing 22½ months, the controls gained 552 g in weight, whereas, the exposed group gained 2116 g.

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 tattoo. All three species were individually housed during the 6-hr 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 hr/day. The exposed animals were also housed in the animal quarters except during the 6-hr 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

Table 1. Results of pulmonary function tests in monkeys after 14 months exposure to PVC dust.[a]

Pulmonary function test	Groups	
	Control	Exposed
RL, cm H_2O/L/sec	12.1 ± 4.0	13.8 ± 1
CL, ml/cm H_2O	22.9 ± 10	17.5 ± 7
TCL, ml	357 ± 39	360 ± 3
VC, ml	334 ± 36	339 ± 3
IC, ml	185 ± 19	210 ± 2
RV, ml	40 ± 10	36 ± 1
RV/TCL, %	11.3 ± 2	9.9 ± 2
FeV 0.5/FVC, %	87.7 ± 5.8	86.5 ± 2
PF, ml/sec	943 ± 91	960 ± 12
FEF 50%, ml/sec	920 ± 91	905 ± 19
FEF, 25%, ml/sec	648 ± 173	656 ± 9
FEF 10%, ml/sec	262 ± 114	269 ± 15
CV, ml	21 ± 9	21 ± 1
ΔN_2/100 ml	1.05 ± 0.3	0.67 ± 0
Visc V, ml	28.7 ± 19	19.9 ± 1

[a]Data are presented as means ± one standard deviation for each of the parameters.

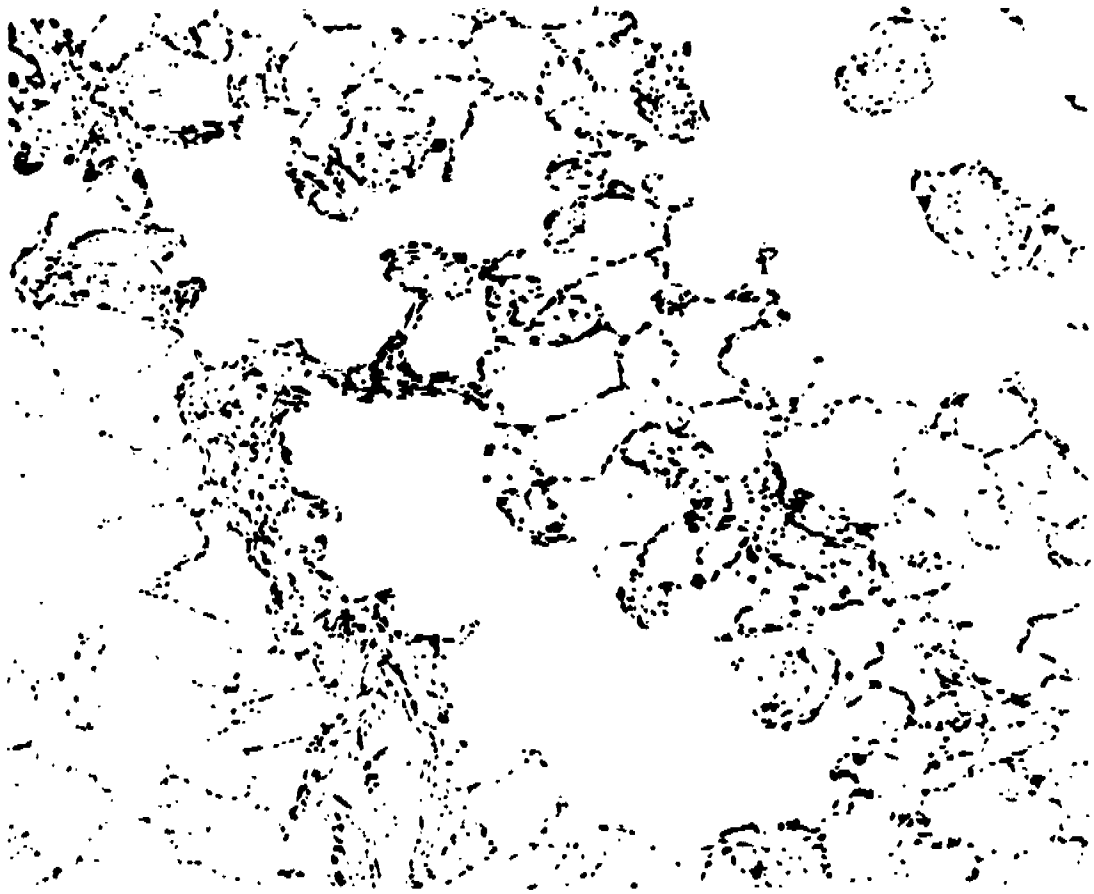

FIGURE 1. Macrophage aggregates in lung of monkey exposed to PVC dust for 22 months. Aggregates are primarily in respiratory bronchioles and alveolar ducts. (Original magnification 40×).

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 hr 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 sec ($FeV^{0.5}$), peak expiratory flow (PF), 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 nonparametric statistical analyses.

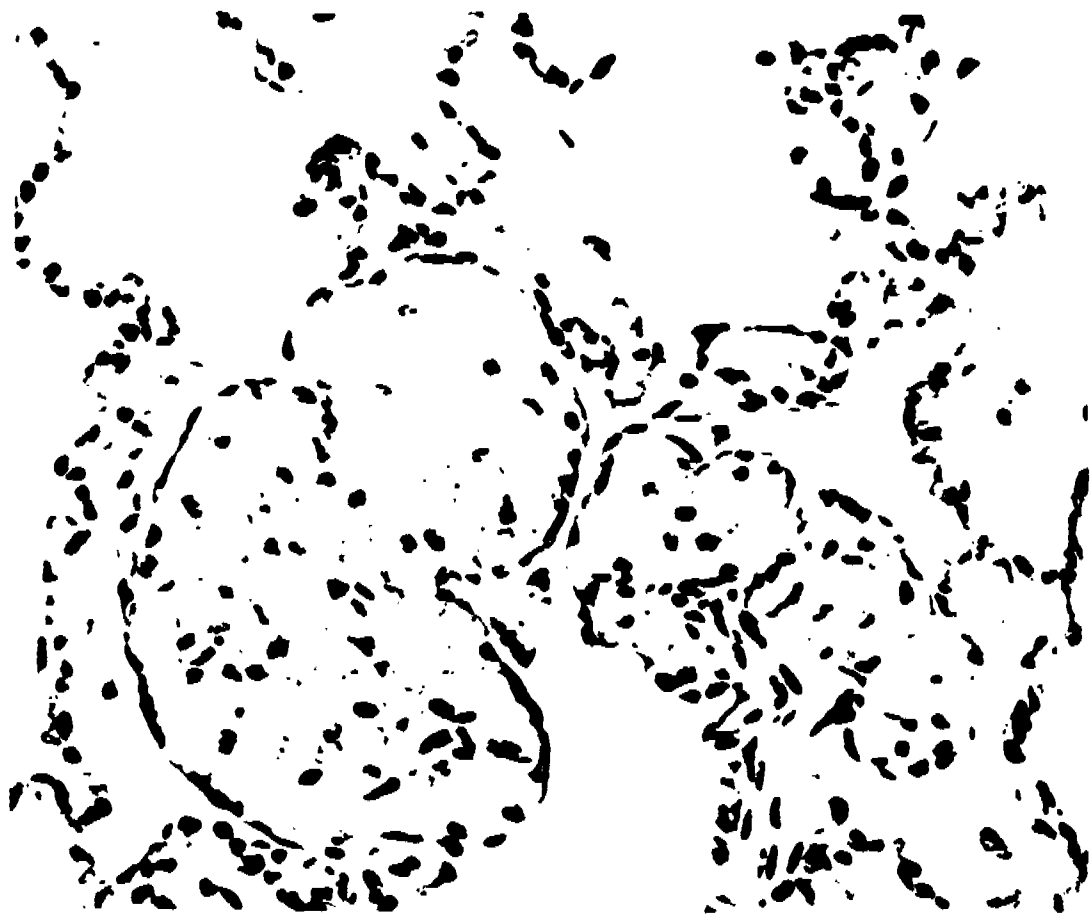

FIGURE 2. Macrophage aggregates in lung of monkey exposed to PVC dust for 22 months. (Magnification 385 ×).

Results

The mean total dust concentration in the chambers for the rodents was 13.0 mg/m³ (SD = 2.34) and for the monkeys 12.9 mg/m³ (SD = 4.69). The mean respirable dust concentration was 10.4 mg/m³ for both the rodents and the monkeys. The monkeys were exposed on 464 days for a total of 2818 hr, while the rodents were exposed on 245 days for a total of 1426 hr.

The vinyl chloride concentrations in the chambers at the two sampling periods were 0.01 and 0.02 ppm. A small nonquantified 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 be-

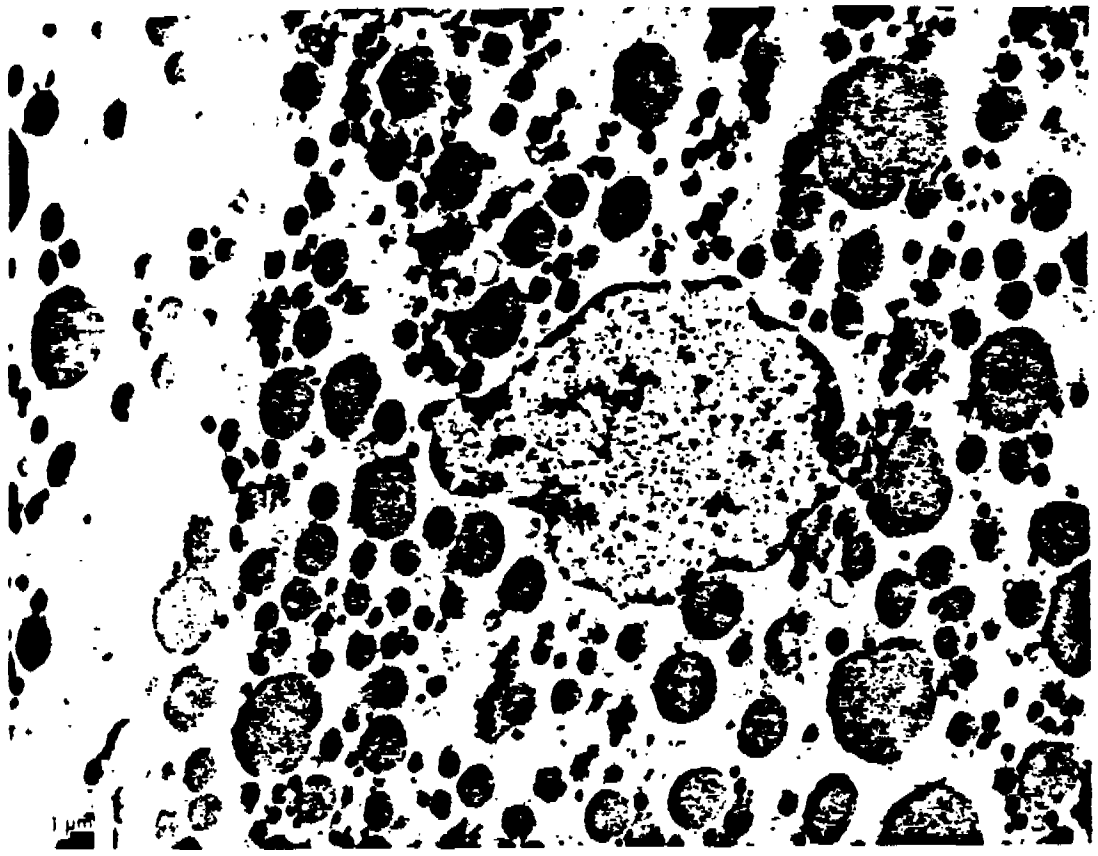

FIG. 3. Transmission electron micrograph of a macrophage from the lung of a monkey exposed to PVC dust for 22 months. Note the numerous round and oval, electron dense particles comprising most of the cytoplasmic space. These are the inhaled PVC particles.

tween 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 g and that of the exposed animals was 4190 g. 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 ten control monkeys were autopsied 22[illegible] 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 (Fig. 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 three to seven per microscopic field at 100 × 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

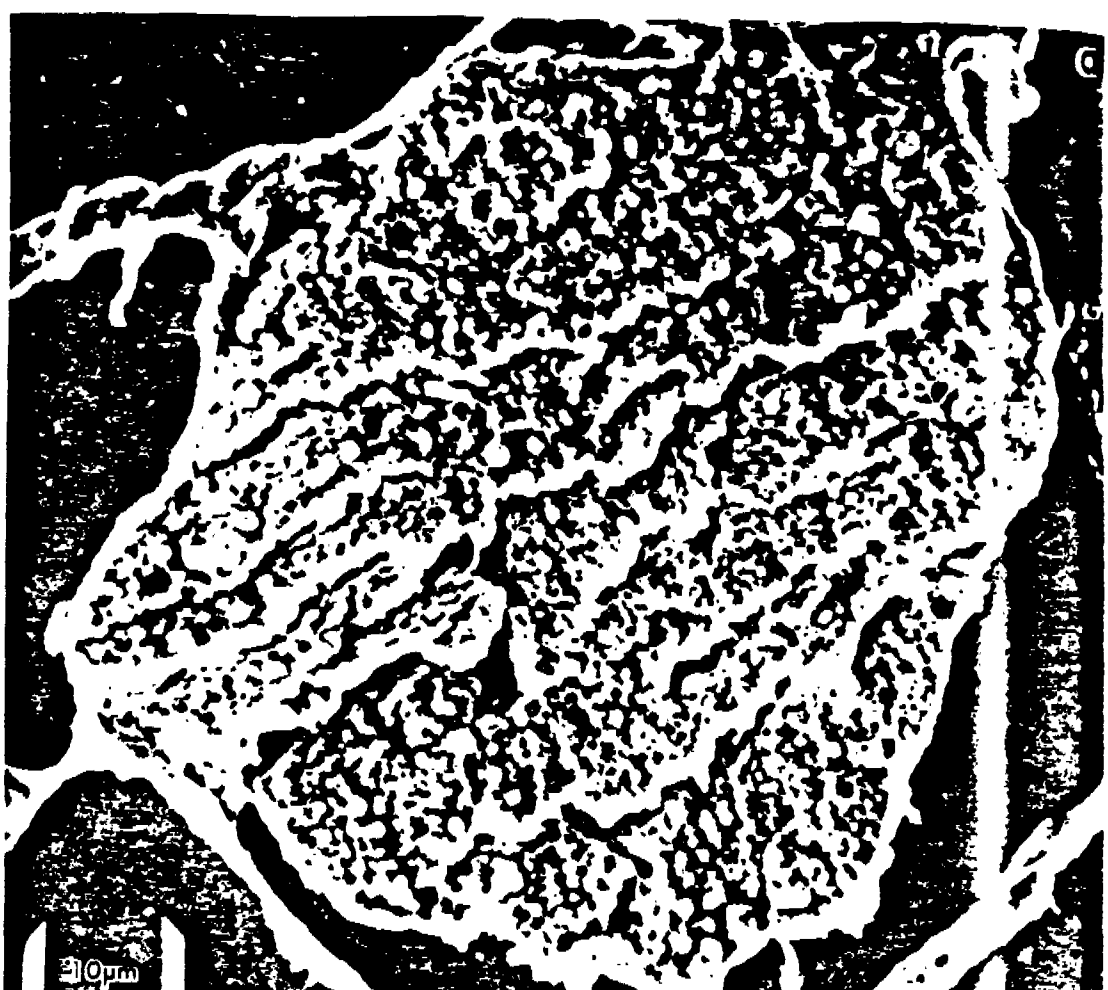

FIGURE 4. Scanning electron micrograph of a 5-μm section of lung of monkey exposed to PVC dust for 22 months. This photo shows the numerous PVC particles which obscure the cellular outlines of the macrophages in which they are residing.

and were of the same size and shape as PVC particles (Fig. 3). Analysis of these particles with the microprobe revealed high concentrations of chlorine (Fig. 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.

The 57 exposed and 64 control rats were autopsied 12 months after initiating exposures. Microscopic examination of the lungs of the exposed animals revealed 0–3 macrophage aggregates/microscopic field at 100× magnification (Fig. 6). These aggregates were smaller and much less frequent than those seen in the monkey lungs. Chronic pneumonitis, typical for rats, was present with equal severity and frequency in the control and exposed rats. No treatment related lesions were seen in sections of the other organs examined.

The 36 exposed and 39 control guinea pigs were autopsied 12 months after initiating exposures. Light microscopic examinations of the lungs of exposed guinea pigs revealed fewer collections of giant macrophages with clear foamy cytoplasm than those

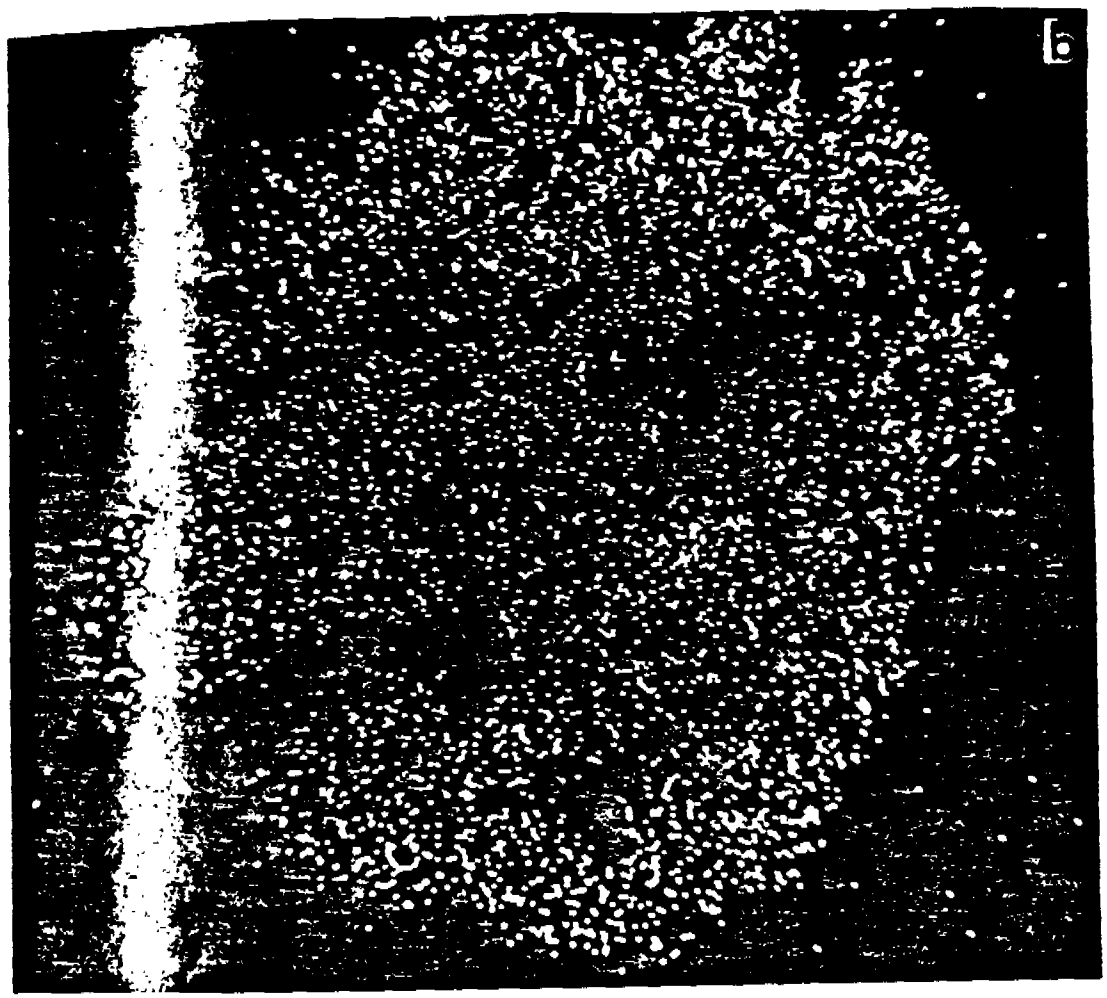

FIGURE 5. Chlorine x-ray map of the same area and magnification depicted in Fig. 4. The white dots indicate the presence of the element chlorine. Note that the dots are clustered in the same area as the PVC particles, thus confirming the identification of the PVC particles

seen in the exposed monkeys or rats. Interstitial lymphocytic pneumonia was a constant finding in most of the exposed and control animals, and the severity and incidence were not related to treatment. Few macrophage aggregates similar to those seen in the lungs were present in the tracheobronchial lymph nodes of the exposed guinea pigs. No treatment-related lesions were seen in sections of the other organs examined.

Discussion

The monkeys in this study developed a benign, simple pneumoconiosis resulting from the inhalation of PVC dust at a mean concentration of 13 mg/m^3 for 464 days (2818 hr). The cellular response visible at 22 months of exposure consisted of PVC-laden macrophages aggregated into clusters in the lungs. On the other hand, the lungs of the rats and guinea pigs contained very few macrophage aggregates and in a much lower concentration than in the monkey lungs. This difference in degree of cellular response could possibly be explained on the basis of fewer PVC particles being deposited in the lungs of these rodents.

Rodents at rest in the chambers during the day breathe exclusively through their noses. Monkeys under the same conditions do not. The rodents in this experiment had extensive bronchitis and

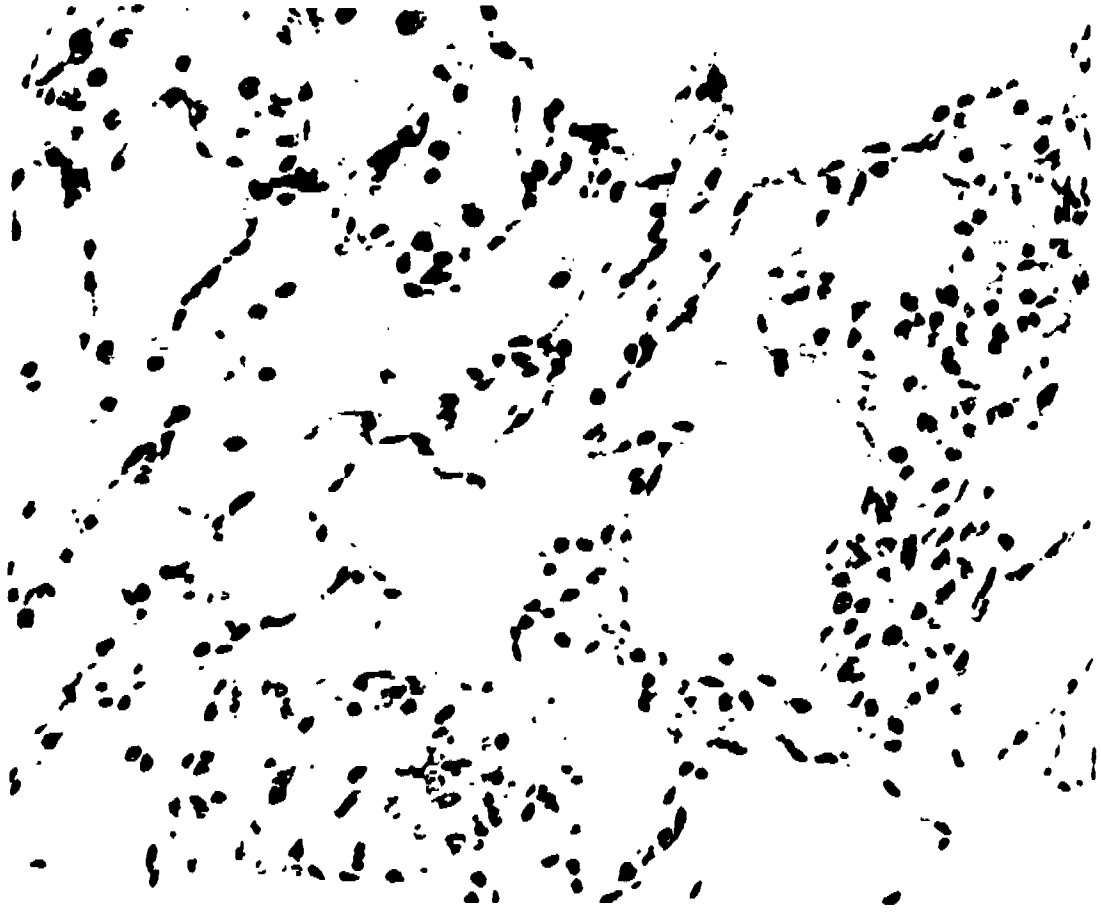

FIGURE 6. Macrophage aggregates in the lung of a rat exposed to PVC dust for 12 months. Note vacuolated appearance of cel. (Magnification 385 ×).

pneumonitis, whereas the monkeys did not. Both nose breathing and bronchitis are factors which reduce the percentage deposition of inhaled particles in the alveolar regions of the lungs.

Two studies have been published on the pathological effects of inhaled PVC in rats (*7*, *8*). In one study (*7*) rats and guinea pigs were placed in a PVC bagging facility. Two guinea pigs and an unstated number of rats were autopsied 2, 4 and 7 months after their continuous residence in the facility. Although the animals developed pulmonary diseases, the small number of animals studied and the lack of adequate controls makes it impossible to assess the significance of the exposure to PVC. In the other study (*8*) rats exposed to high concentrations (97 gm/m^3) of PVC dust in a static air chamber for 1 hr/day for up to 12 months developed bronchiectasis, emphysema, purulent pneumonia, lung abscesses and squamous metaplasia in bronchial epithelium. Although the control rats were free of these diseases, there were only 10 controls examined. In view of the propensity for rodents (controls) to contract acute and chronic pulmonary diseases, the experimental conditions under which control animals are kept is extremely important, and should be stated in the protocol. No mention of this was made in that experiment.

Two cases reports showing granulomas in lungs of two PVC workers have been reported (*3*, *5*). Except for the more closely packed macrophages in the lesions shown by Aranaud et al. (*5*), 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 hr 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. (*3*) 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. (*6*) 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 pathological diagnosis of a benign pneumoconiosis.

The authors wish to acknowledge the assistance of the following people in this project: George Madden, Brandon Barton, John Clark, David Brewer, Margrit Stoll, Myra Springs, Hazel Patterson, Lea Kalejs, Ardith Grote, John Holtz, Charles Goraki, Richard Niemeier, Richard Hornung and Patricia Combs.

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Preliminary Observations of the Effect of Inhalation of PVC in Man and Experimental Animals

by J. C. Wagner* and N. F. Johnson*

Attention has been focussed, both in man and experimental animals, on the effects of inhalation of the gas monomer, vinyl chloride. Recently, note is being taken of the possible effects of the inhalation of the polymer in man. The particles in question are those produced commercially as paste polymer or dispersion polymer or having an average diameter of 0.15 μm, and accounting for more than 10% of the production in Britain. There are now strict regulations for the control of the monomer gas, but the particles are regarded as nuisance dust and their emission is not covered by specific legislation.

Our studies on rats, where both inhalation and implantation methods of exposure have been used, and examination of tissue from human cases exposed to paste polymers, indicate that these small particles can only be regarded as evidence of exposure, and on present evidence there is no indication of causation of significant pulmonary disease. Techniques have been developed by which these particles can be demonstrated in ordinary histological preparations and by transmission electron microscopy.

The finer particles of PVC known in the United States as dispersion polymer, are usually less than 1 μm in diameter. During the last five years we have conducted a number of preliminary investigations using this material, and have also observed these small particles in the lungs of men exposed to this type of PVC, and have recovered these particles from the lungs and livers of human cases using maceration techniques. A second series of experiments has been started but no results are available.

The recognition of PVC in tissue has been greatly facilitated by a staining method developed by Wilson (1). Normally processed histological sections are stained with a Sudanophilic dye, which stains the particles a bright red. As the tissue has been processed and all lipid removed, only the PVC and some other related plastics will stain. The particles can also be recognized under the transmission electron microscope, and the morphological appearances supported by the confirmation of the presence of chloride when examined by x-ray microanalysis.

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Animal Experiments

Experiment 1

The experimental animals were caesarean-derived, barrier-maintained rats of the I.C.I. Alderley Park Wistar strain. Six-week old rats were randomized, with equal numbers of each sex, and inoculated intrapleurally by using a previously described technique (2). Forty-eight animals received 20 mg of PVC dispersion polymer into the right pleural cavity. The control animals were inoculated in a similar manner (Table 1). The rats were allowed to live out their lives and all are now dead.

Between 12 and 18 months after inoculation, nine of the animals receiving the PVC died. Of these, five had tumors of the liver and one had a tumor originating from the site of inoculation. None of the other animals injected with PVC, nor any of the control animals, had a tumor of this type. These tumors were shown to pathologists in Britain and the United States. It was generally agreed that they were poorly differentiated sarcomas, and in three of the animals, the possibility of Kupffer cell origin was considered. As no other animals devel-

Table 1. Intrapleural inoculation (rats 6 weeks old).

No. rats	Treatment
48 rats	20 mg PVC in saline
24 control rats	20 mg UICC crocidolite in saline
24 control rats	20 mg Min-U-Sil (quartz) in saline
24 control rats	saline

oped these tumors, two further experiments have been started. In the first, dispersion polymer from three British manufacturers was used, and in the second, freshly produced dispersion polymer from two sources has been inoculated, as well as similar material from which all evidence of detergent or vinyl chloride monomer has been removed. These investigations are still in progress, but in the first of these studies, the animals have passed the 18 month period without any occurrence of the tumors.

Inhalation Studies

A group of 48 rats, 24 of each sex, of the same stock as used in the previous experiments were exposed in an inhalation chamber to PVC dust, the apparatus and methods being the same as previously described (*3*). The animals were exposed to dispersion polymer, at a concentration of 12 mg/m^3 for 7 hr/day, 5 days/week, for 5 months. There were also 48 nonexposed controls. The cumulative dose of the exposed rats was 8552 mg/m^3 (Table 2). Six rats from each group were killed at the end of the exposure, and a further six a year after the start of the exposure. The remaining animals were allowed to survive until they died of natural causes.

Table 2. Inhalation study.

No. of rats	Exposure
48 rats 6 weeks old	22 weeks, 12 mg/m^3; cumulative dose 8552 mg/m^3 -hr
48 control rats	None

The PVC particles were present in the macrophages within the alveoli arising directly from the respiratory bronchioles immediately after the exposure. The distribution of these accumulations was widespread but less than a third of the primary units were involved. Occasional dust particles were observed in sections from the bronchopulmonary lymph glands, the Kupffer cells in the liver and in the spleen. At the end of a year, the dust was still present in the spleen and around some foci of macrophages there was evidence of a slight proliferation of reticulin fibers. This early dust reticulination did not show evidence of progression in any of the other animals, some of which survived for more than two years after the initial exposure.

Experience with Human Tissue

We have had the opportunity of examining a limited amount of human tissue. This included three cases of accepted angiosarcoma of the liver, a man with severe hepatic fibrosis who underwent a subsequent porto-caval shunt and material from people who had been employed in a PVC factory. These people had either had pulmonary biopsies or had died of diseases unconnected with their occupation. In all but one case we found small amounts of PVC in the lung tissue. In two of three angiosarcomas particles of PVC were found after the maceration of the liver tissue.

At this stage of the investigation, these particles can only be regarded as evidence of exposure to dispersion polymer.

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Results of Sputum Cytology among Workers Exposed to Vinyl Chloride Monomer and to Poly(vinyl Chloride)

by Cesare Maltoni* and Paola Lodi*

The results of systematic cytological sputum examinations of 3,380 Italian VC-PVC industry workers and of 2,287 workers in other industries at different potential risk and chosen as control groups are reported.

The results indicate an increase in cellular abnormalities and dysplasias in the epithelium of the respiratory tract among VC-PVC workers. These data are in line with experimental results showing that VC produces lung tumors in mice and with early epidemiological evidence among exposed workers.

Introduction

In 1975, it was decided to include the cytological examination of sputum in the protocol of systematic medical surveillance of the workers in all the Italian plastic factories exposed to vinyl chloride (VC) and poly(vinyl chloride) (PVC).

This program was co-sponsored by the Italian Federation of Unions of Chemical Workers (FULC) and by the Public Health Service of the Italian regions where the factories were located.

The decision to investigate cytologically all Italian VC-PVC industry workers was taken on the basis of the following facts: (1) the observation of a marked increase in the incidence of lung adenomas in mice exposed by inhalatory route, to a spectrum of doses of VC ranging from 10,000 down to 250 ppm (*1-3*); (2) the unusual finding of cellular abnormalities in a high portion of the lung adenomas of exposed mice (*1-3*); (3) the observation of frequent severe abnormalities (squamous dysplasia and atypical adenomatous hyperplasia) in the sputa of a small group of heavily exposed workers (*3*); (4) the report of some increase in lung carcinomas among workers from two VC-PVC factories (*4*); (5) the finding that the majority of lung carcinomas observed among exposed workers were not of a common histotype i.e., giant cell carcinomas (*5*).

Planning and Methods

The investigation was carried out on workers from 13 Italian VC-PVC factories located in the northern, central and southern parts of Italy, namely, in Villadossola (1), Portomarghera (3), Bollate (1), Ferrara (1), Ravenna (1), Rosignano (1), Terni (1), Brindisi (1), Ferrandina (1), Porto Torres (1) and Cagliari (1).

A total of 3380 workers was examined. These workers have been and/or are exposed to the monomer and part of them also to PVC dust. For comparison 2287 workers in other industries at different potential risk were examined: namely, workers manufacturing PVC products, workers in chemical industries not dealing with plastics, metal workers, miners and workers in the chromium industry.

For each sputum examination four cytological slides were prepared. The smears were stained by the Papanicolaou technique.

The slides were screened and evaluated independently by the pathologists of the hospitals in the area where the factories were located, then by a trained cytologist in our institute. All abnormal smears were reviewed by the senior pathologist of

*Institute of Oncology and Tumor Center, Bologna, Italy.

Table 1. Type, sequence and classification of local changes in the genesis of the various histotypes of pulmonary carcinoma

Stage					Cytologic class
		Normal respiratory epithelium			
		Nonciliated cuboid epithelium			
Initial nonspecific stage		Adenomatous hyperplasia	Squamous metaplasia	Basal cell hyperplasia	II, II-(III) II-III
Intermediate specific state		Atypical adenomatous proliferation	Squamous dysplasia	Basaloid cell dysplasia	(II)-III, III, III-IV
Tumor stage	Preclinical tumor	*In situ* adenocarcinoma	*In situ* squamous carcinoma	*In situ* anaplastic carcinoma	IV and V
	Clinical tumor	Invasive adenocarcinoma	Invasive squamous carcinoma	Invasive anaplastic carcinoma	

Table 2. Classification, characterization, distribution by classes and code of sputum cytology findings.

Class	Cell character: Type[a]	Degree	Quantity	Code
Not performed				99
I	Normal epithelium (LRE, URE, OCA)		1, 2, 3	01
	Histocytes		1, 2	
I-II	Normal epithelium (LRE, URE, OCA)		1, 2, 3	02
	Histocytes		3	
II	Squamous metaplasia LRE	+/+ +	1, 2, 3	03
	Hypersecretive mucous cells			
II-(III)	Squamous metaplasia LRE	+ + +	1, 2, 3	04
	Adenomatous hyperplasia LRE			
II-III	Mild atypical adenomatous hyperplasia LRE		1	05
	Mild squamous dysplasia LRE		1	
	Mild dysplasia URE, OCA		1	
(II)-III	Mild atypical adenomatous hyperplasia LRE		2, 3	06
	Mild squamous dysplasia LRE		2, 3	
	Mild dysplasia URE, OCA		2, 3	
III	Well defined atypical adenomatous hyperplasia LRE			07
	Well defined squamous dysplasia LRE			
	Well defined dysplasia URE, OCA			
III-IV	Grave atypical adenomatous hyperplasia LRE			08
	Grave squamous dysplasia LRE			
	Grave dysplasia URE, OCA			
IV	Suspected Adenocarcinoma			09
	Suspected Squamous carcinoma			
	Suspected Undifferentiated carcinoma			
V	Adenocarcinoma			10
	Squamous carcinoma			
	Undifferentiated carcinoma			
Not evaluable				11

[a]LRE = lower respiratory epithelium; URE = upper respiratory epithelium; OCA = oral cavity.

Table 3 Incidence of various types of cytological changes in sputa: comparison of results among VC-PVC workers and workers of the reference groups.

	No of cases	Non-evaluable cases (insufficient material)	Evaluable cases	Cases without epithelial changes		Cytological changes: Hyper-secretive mucous cells and squamous metaplasia LRE +/+ +		Squamous metaplasia LRE + + +		Squamous metaplasia with horn pearls LRE		Adenomatous hyperplasia LRE		Atypical adenomatous hyperplasia LRE		Squamous dysplasia LRE		Dysplasia URE, OCA	
				No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Workers of VC-PVC industry	3380	822	2558	799	31.2	1158	45.1	374	14.6	70	2.7	794	31.0	38	1.5	219	8.6	44	1.7
PVC manufacturers	422	79	343	99	28.9	258	73.8	36	10.5	1	0.3	74	21.6	4	1.2	4	1.2	1	0.3
Workers of various chemical industries[a]	1019	130	889	165	18.6	604	66.9	83	9.3	3	0.3	227	25.5	8	0.9	10	1.1	–	–
Metal workers	264	54	210	73	34.8	109	51.9	30	14.3	1	0.5	5	2.4	–	–	6	2.8	–	–
Miners	402	48	354	47	13.3	254	71.7	41	11.6	1	0.3	59	16.7	5	1.4	4	1.1	1	0.3
Workers of chromium industry	180	28	152	9	5.9	89	58.5	69	45.4	1	0.6	7	4.6	6	3.9	28	18.4	–	–

[a] Other than VC-PVC and chromium industries and not exposed to a known risk.
[b] Not exposed to a known risk.

Table 4 Distribution, by classes of cytological changes in sputa: comparison of results among VC-PVC workers and workers of the reference groups.

	No of cases	Not evaluable cases (insufficient material)	Evaluable cases	Classes: I, I-II		II		II-(III)		II-III		(II)-III		III		III-IV		IV		V	
				No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Workers of VC-PVC industry	3380	822	2558	799	31.2	705	27.5	780	30.4	211	8.6	21	0.8	35	1.3	7	0.2	–	–	–	–
PVC manufacturers	422	79	343	99	28.9	135	39.3	102	29.7	4	1.2	1	0.8	1	0.3	1	0.3	–	–	–	–
Workers of various chemical industries[a]	1019	130	889	165	18.6	399	44.8	313	35.2	6	0.7	6	0.7	–	–	–	–	–	–	–	–
Metal workers	264	54	210	73	34.8	102	48.6	28	13.3	6	2.8	–	–	1	0.5	–	–	–	–	–	–
Miners	402	48	354	47	13.8	220	62.1	82	23.1	2	0.6	1	0.3	1	0.3	1	0.3	–	–	–	–
Workers of chromium industry	180	28	152	9	5.9	63	41.5	51	33.6	18	11.8	2	1.3	5	3.3	4	2.6	–	–	–	–

[a] Other than VC-PVC and chromium industries and not exposed to a known risk.
[b] Not exposed to a known risk.

Table 5. Distribution of classes II-(III) and over among VC-PVC workers and the workers in reference groups.

	Classes II-(III), %	Classes II-III, (II)-III, %	Classes III, III-IV, %
Workers of VC-PVC industry	30.4	9.4	1.5
PVC manufacturers	29.7	1.5	0.6
Workers of various chemical industries	35.2	1.4	–
Metal workers	13.3	2.8	0.5
Miners	23.1	0.9	0.6
Workers in chromium industry	33.6	13.1	5.9

the same institute. A joint critical reevaluation was carried out for those cases where there was not full agreement.

The same criteria of classification of the lesions and their distribution by classes were adopted by all pathologists.

Such criteria are based on our knowledge of the local cytological changes and of their sequence in the genesis of the various histotypes of pulmonary carcinomas (Table 1).

The list of the most relevant changes correlated with environmental and occupational exposure, their distribution by classes following qualitative and quantitative parameters, and the code, are given in Table 2. This list takes into account not only cells from the pulmonary tree, but also cells from the upper respiratory tract and oral cavity.

Results

The number of valuable cases, the distribution of the cytological changes and the distribution of the results expressed by classes in the group of workers in the VC-PVC industries and in the control groups, are given in Tables 3 and 4. The incidence of dysplastic changes is particularly high in the plastics industry workers when compared to the other control groups, with the exception of chromium workers, which can be considered a positive control. The situation is well illustrated by the distribution of classes II-(III) and above (Table 5).

It may be stated that, in relation to the incidence of respiratory cell abnormalities, the workers in the VC-PVC industries can be placed halfway between chromium workers and other groups.

A finding which deserves attention is the occurrence of atypical cells in the oral cavity and upper respiratory tract in 44 workers (17%) among VC-PVC workers (Table 3).

The results were highly homogeneous in different factories, suggesting that variations in climate, which may affect the incidence of common pneumopathies, is not a determining factor.

The difference in the distribution of the pathological findings was not dependent on tobacco smoking.

Conclusions

The results presented are consistent with experimental data and early epidemiological evidence on the potential oncogenic effects of VC exposure on the lungs.

Furthermore, our data suggest a possible oncogenic risk for the upper respiratory tract which should now be explored by proper epidemiological investigation.

Much remains to be done to clarify the part played by the monomer and by polymer dust in determining the observed cytological changes. Our data are now being re-examined, on the basis of the complete exposure history of single workers, to better establish the role played by PVC particles.

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Observations of the Site-Specific Carcinogenicity of Vinyl Chloride to Humans

by Peter F. Infante*

A review of epidemiologic studies of workers exposed to vinyl chloride (VC) was conducted. Some of these studies comprised small cohorts and thus were insensitive in the evaluation of carcinogenic response for sites that do not demonstrate a high relative risk. Other larger studies used methodology and design that precluded an interpretation of the results. Such limitations were acknowledged by some authors.

Use of restrictive disease rubrics also lead to the submerging of sites that would have demonstrated significant excesses. For example, some investigators analyzed data for liver cancer deaths with the board category of digestive system cancer deaths, while others combined data for CNS cancer deaths with the broad cateogry of "other and unspecified cancer," and most studies analyzed information for lymphatic and hematopoietic system cancer deaths with all data combined. Only four of eight studies reviewed could demonstrate a significant excess of liver cancer among VC-exposed workers—a site confirmed in humans by 1974. In contrast, five of eight studies appear to demonstrate a significant excess of CNS cancer mortality. Workers exposed to VC also demonstrate a significant excess of mortality for lung cancer, while the data for lymphatic and hematopoietic system cancer are suggestive. Interpretation of cancer of the latter systems may have been clarified if investigators had not analyzed their data by broad disease classifications.

In 1930, shortly after vinyl chloride (VC) was introduced into commerce, VC toxicity was reported in experimental animals (*1*). Over the next two decades, study throughout the world indicated that employment in the VC industry was associated with a wide range of toxicity in humans. This toxicity has included nonmalignant pathologic effects or symptoms, involving (but not limited to) the bones, liver, central nervous system (CNS), lungs and blood (*2*).

Between 1970 and 1974, experimental bioassay demonstrated VC-induced cancer in multiple organs including the liver, brain, lungs and lymphatic system (*3, 4*). This carcinogenic response has been observed in several species, given a wide range of doses, by various routes of administration.

Between 1973 and 1977, several epidemiologic studies were undertaken to assess the site-specific cancer risk among workers exposed to VC. For this presentation, findings of these studies will be limited to an assessment of cancer of four organs or organ systems in humans. These same sites are known to be associated with nonmalignant VC-related disease or symptoms in humans and cancer in experimental animals.

Liver Cancer in Humans

Table 1 shows a summation of data from the epidemiologic studies as related to liver cancer. Some authors did not present site-specific analyses for liver cancer deaths. Therefore, the most specific information available is presented.

Waxweiler et al. (*5*) conducted a cohort study of workers who had been exposed to VC in the U.S.

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The views expressed in this paper do not necessarily represent those of the Occupational Safety and Health Administration.

Table 1. Epidemiologic study results of VC-exposed workers as related to biliary and liver or digestive system cancer deaths

Investigation	Site	Deaths		
		Observed	Expected	SMR
Waxweiler et al. (5)	Biliary and liver			
Total cohort		7	0.6	1155[a]
Latency > 15 yr		7	0.4	1606[a]
Byren et al. (6)	Liver and pancreas			
Total cohort		4	0.97	413[b]
Latency > 10 yr		4	0.68	589[b]
Fox and Collier (7)	Liver			
Total cohort		4	1.64	244
Plant #2 > 15 yr		3	0.13	2308[a]
Seven other plants		1	1.51	66
Monson et al. (8)	Biliary and liver			
Total deaths		8	0.7	11.0[b,c]
Tabershaw and Gaffey (9)	Digestive organs			
Total cohort		19	21.7	94
Highest exposure, > 5 yr employment		11	7.5	151
Buffler et al. (10)[d]				
Ott et al. (11)[e]				
EEH (12)	Digestive organs			
Total cohort		29	40.8	71
Latency > 20 yr		9	13.6	70

[a] $p < 0.01$.
[b] $p < 0.05$.
[c] Proportional mortality study risk ratio.
[d] No liver cancer identified among 8 cancer deaths.
[e] No liver cancer identified among 20 cancer deaths.

for at least five years and who had achieved a period of ten or more years since initial exposure (latency). On the basis of seven liver and biliary cancer deaths that fit the cohort definition, the study demonstrated an 11-fold to 16-fold excessive risk of death from cancer of this site among VC-exposed workers. These findings represent an underestimate of the risk because seven additional individuals who died from liver/biliary cancer at the plants being studied were not included in the analyses. Of these latter seven cases, four individuals diagnosed with liver angiosarcoma were still alive at the study cut-off date, while two individuals who died from biliary cancer had incomplete information on length of exposure to VC. A seventh individual did not fit the study cohort definition as he was exposed for only three years. He died from liver angiosarcoma 17 years after his initial exposure to VC.

Byren et al. (6) conducted a cohort study of all Swedish workers ever employed in positions where exposure to VC could have occurred. The investigators combined deaths from cancer of the liver and pancreas because they believed that there was some overlap in reporting. There were four liver/pancreatic cancer deaths observed, compared to 0.77 expected ($p < 0.02$). An additional death from liver angiosarcoma was identified as having occurred after the study cut-off date and thus was not included in the study.

Fox and Collier (7) studied U.K. workers exposed to VC. In eight factories studied, they observed a total of four liver cancer deaths as compared to 1.64 expected. Three of these deaths occurred in factory 2, where only 0.13 would have been expected ($p < 0.01$). The authors stated that it was difficult to identify angiosarcoma of the liver from death certificates (the usual method of identification), since some of these deaths were classified as primary, some as secondary liver cancer, and others were not certified as cancer deaths at all.

The results from the Fox and Collier study probably represent an underestimate of the observed risk of death from cancer for the following reasons: (1) 75% of the study cohort was employed for less than ten years; (2) only 8% of the cohort was employed for more than 20 years; and (3) even

for those who completed 20 years of service, the authors stated that "because their service has only recently been completed, the follow-up period is too short to evaluate the carcinogenic effect of VCM." This statement obviously applies to the liver as well as to other sites.

Monson et al. (*8*) conducted a proportional mortality study of 161 deceased workers from two plants where VC was used. These plants were also studied by Waxweiler et al. (*5*). They observed eight deaths from liver and biliary tract cancer versus 0.7 expected; the risk ratio was 11.0.

Tabershaw and Gaffey reported the results of a cohort study of workers exposed to VC in 33 U.S. industrial facilities. The authors did not analyze the data separately for liver and biliary cancer. Thus, deaths for these causes are accounted for in the category of digestive organ cancer. As noted in Table 1, for the total cohort there were 19 deaths from digestive organ cancer and 21.7 expected. For the highest exposure cohort, with more than five years of exposure, there were 11 digestive organ cancer deaths observed versus 7.5 expected. None of the observations are statistically significant.

However, the risk of liver cancer in this cohort is submerged by including data for this cause of death in the analysis with digestive organ cancer deaths. Of the 19 digestive cancer deaths, the authors noted that seven were from liver cancer. Two of these liver cancer deaths were listed as angiosarcoma according to the diagnosis on the death certificate. An additional four deaths from liver angiosarcoma were identified in this cohort by the time the study was published in 1974. Two of these deaths had been categorized by death certificate diagnosis as primary liver cancer, and two had been certified under causes of death other than cancer, i.e., cirrhosis of the liver and hepatoma.

This study again demonstrates one of the inherent limitations of epidemiologic studies (incorrect diagnosis in relatively rare causes of death) that result in an underestimate of the relative cancer risk. An additional factor, indicated by the authors, that may have led to an underestimate of the risk in this study was that the group with no vital status determination, 15% of the population, began their exposure ten years before the group for whom followup was completed. As a result, some individuals with longer latency periods were omitted from the study. In addition, 57% of the cohort actually studied had less than 15 years of latency. Because of the healthy worker effect, the authors appropriately stated that SMRs higher than expected may be worthy of attention even if they are not statistically significant.

Buffler et al. (*10*) and Ott et al. (*11*) did not observe any liver cancer deaths among eight and twenty deaths, respectively, in their studies.

An unpublished study conducted by Equitable Environmental Health (*12*) reported the mortality of a cohort of workers from 37 U.S. industrial facilities. This study included data for the facilities studied by Tabershaw and Gaffey (*9*). Data were not analyzed separately for liver cancer. However, the category of death from cancer of the digestive organs, which includes liver cancer deaths, indicates a deficit of mortality. As shown in Table 1, even for those individuals who had achieved 20 or more years of latency, the SMR was only 70. It is somewhat unusual to observe such a deficit of mortality among workers who had achieved such a long latency period.

Brain Cancer in Humans

Brain cancer also has been associated with exposure to VC. A summary of the results of mortality studies is shown in Table 2. Although the number of cases upon which observations were based are small, Waxweiler et al. (*5*) and Byren et al. (*6*) demonstrated significant excesses of brain cancer. The relative risks were five and six, respectively. Waxweiler et al. (*5*) also noted an unusual distribution in the cell type of brain cancer. Of 10 brain cancer deaths identified among the VC-exposed workers, nine (90%) had a histologic diagnosis of glioblastoma multiforme. The tenth case had no confirmation of cell type. The authors contrasted this high proportion with that of the Yale autopsy series in which 33% of primary intracranial neoplasms were glioblastoma multiforme.

Fox and Collier (*7*) observed two brain cancer deaths as compared to 3.7 expected for the entire cohort. For those cohort members categorized as having high exposure, one brain cancer death was observed versus 0.4 expected. Monson et al. (*8*) demonstrated a fourfold risk of brain cancer.

Tabershaw and Gaffey (*9*) categorized brain cancer with "other and unspecified causes of cancer death;" therefore, it is not possible to determine the actual brain cancer risk identified in this study. Since the Tabershaw and Gaffey study (*9*) was a subset of the EEH study (*12*), the latter study was used to estimate the expected number of brain cancer deaths in the former study under the assumption that the age distributions were similar. The proportion of expected brain cancer deaths from "other and unspecified cancer deaths" in the EEH study (*12*) was then applied to the expected from this same category in the Tabershaw and

Table 2. Epidemiologic study results of VC-exposed workers as related to central nervous system.

Investigation	Site	Deaths		
		Observed	Expected	SMR
Waxweiler et al. (5)	Brain and CNS			
Total cohort		3	0.9	329
Latency > 15 yr		3	0.6	498[a]
Byren et al. (6)	Brain			
Total cohort		2	0.3	612[a]
Fox and Collier (7)	Brain			
Total cohort		2	3.7	55
Highest exposure		1	0.4	278
Monson et al. (8)	Brain			
Total deaths		5	1.2	4.2[a,b]
Tabershaw and Gaffey (9)	Other and unspecified			
Total cohort		17	11.8	155
Highest exposure, > 5 yr employment		7	3.5	204
All exposure levels	Brain	6	2.4[c]	250[a]
Buffler et al. (10)[d]				
Ott et al. (11)	All sites other than			
Total cohort	digestive and respiratory	6	6.8	88
Total cohort	Brain	2	0.7[c]	286
EEH (12)	Brain and CNS			
Total cohort		12	5.9	203[a]

[a] $p < 0.05$.
[b] Proportional mortality study risk ratio.
[c] Estimated.
[d] No brain cancer identified among 8 cancer deaths.

Gaffey study (9). As a result, 2.4 brain cancer deaths were estimated to have been expected and compared to six observed in the study. This difference is significant.

Buffler et al. (10) did not identify any deaths from brain cancer in their small cohort. Ott et al. (11) did not analyze their data separately for brain cancer, but rather included brain cancer deaths with cancer deaths from "all sites other than digestive and respiratory." Therefore, using an analytical technique similar to that described above, the proportion of expected brain cancer deaths among "all sites other than digestive and respiratory" from the EEH study (12) was applied to the expected in the study by Ott et al. (11). As shown in Table 2, there was a resultant estimated 0.7 brain cancer deaths expected as compared to two observed. The excess risk is estimated to be about threefold. The EEH study (12) also demonstrates a significant excess brain cancer among workers occupationally exposed to VC. In summary, the data for brain cancer appear to be more consistent between studies than the data for liver cancer, although the magnitude of the excessive risk is not as great for brain cancer.

Lung Cancer in Humans

As shown in Table 3, Waxweiler et al. (5) observed 11 lung cancer deaths as compared to 5.7 expected ($p < 0.005$) for cohort members who had achieved 15 or more years of latency. The authors also noted what appeared to be an unusual distribution in the histologic types of lung cancer. Of eight histologically confirmed lung cancer cases, five were classified as large cell undifferentiated, and three were categorized as adenocarcinoma. These cell types are different from those usually associated with a cigarette smoking etiology, i.e., small cell undifferentiated and epidermoid carcinomas.

With the exception of the study by Fox and Collier (7), the remaining studies show excess risks of lung cancer ranging from 7 to 200%. However the reservation expressed by Fox and Collier (7), as mentioned earlier, about the short period of follow-up limits the interpretation of their study. This concern is supported by the observation that the SMR for total mortality was only 75, 75% of what would be expected on the basis of comparison to the standard population.

Table 3. Epidemiologic study results of VC-exposed workers as related to respiratory system cancer deaths.

Investigation	Site	Deaths		
		Observed	Expected	SMR
Waxweiler et al. (5)	Respiratory			
Total cohort		12	7.7	156
Latency > 15 yr		11	5.7	194[a]
Creech et al. (6)	Lung			
Total cohort		3	1.8	168
Fox and Collier (7)	Lung			
Total cohort		46	51.2	90
Highest exposure		2	3.7	54
Wilson et al. (8)	Lung			
Total deaths		13	7.9	1.6[b]
Tatenhaw and Gaffey (9)	Respiratory			
Total cohort		25	22.9	112
Highest exposure, 5 yr employment		12	8.5	144
Buffler et al. (10)[c]	Lung			
Total cohort		5	1.7	289[a]
Long exposure duration		4	1.05	381[a]
Short exposure duration		0	0.45	—
Creech et al. (11)	Respiratory			
Total cohort		7	5.8	121
EEH (12)	Respiratory			
Total cohort		45	44.3	107
Highest exposure		7	5.1	141
Medium exposure		19	17.0	116
Low exposure		19	22.2	92

[a] $p < 0.05$.
[b] Proportional mortality study risk ratio.

Table 4. Epidemiologic study results of VC-exposed workers as related to lymphatic and hematopoietic system cancer deaths.

Investigation	Site[a]	Deaths		
		Observed	Expected	SMR
Waxweiler et al. (5)	(200–205)	4	2.50	159
Latency > 15 yr	(200–205)	3	1.70	176
Fox and Collier (7)	(200–207)	9	9.01	100
Wilson (8)	(200–205)	5	3.4	1.5[b]
Tatenhaw & Gaffey (9)	(200–208, 205)	6	6.06	106
Highest exposure, > 5 years employment		4	1.84	222
EEH (12)	(200–208, 205)	11	10.36	112
Latency > 20 years		4	3.10	136

[a] International Classification of Diseases, 7th Revision.
International Classification of Diseases, 8th Revision.
[b] Proportional mortality study risk ratio.

As shown in Table 3, data from the EEH (*12*) and Buffler et al. (*10*) studies suggested a qualitative dose-response relationship between VC exposure and lung cancer risk. However, retrospective categorization of high, medium and low exposure, as was used in the EEH study (*12*), must be viewed with caution because of the subjective nature of judgment. The study by Buffler et al. (*10*) is particularly noteworthy; within a small cohort of only 464 workers, a fourfold risk of lung cancer was observed. When the investigators examined the effect of smoking, under the extreme assumption that those with unknown smoking habits were smokers, the data still demonstrated a significant

excess of lung cancer (5 observed versus 1.98 expected.)

Cancer of the Lymphatic and Hematopoietic System in Humans

Table 4 summarizes data on cancer of the lymphatic and hematopoietic systems among workers exposed to VC. The relative risks for various studies ranged from 1.0 to 2.2, and none of the results demonstrated a significant excess. Although somewhat suggestive, the data need to be further analyzed by latency period and exposure levels combined. Analysis of data separately for lymphatic cancers and leukemia might also lead to meaningful observations.

Summary

In summary, epidemiologic evidence demonstrates that the carcinogenic effects of VC in humans extend beyond the liver. The brain and lung should also be considered target organs. Some studies indicate that the lymphatic and hematopoietic systems are also involved. These observations in humans are supported by studies demonstrating the induction of cancer of these same sites in experimental animals.

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German Investigations on Morbidity and Mortality of Workers Exposed to Vinyl Chloride

by H. Weber,* W. Reinl,* and E. Greiser†

Two studies on mortality and morbidity of workers exposed to vinyl chloride monomer (VCM) which have been carried out on behalf of the Ministry of Labour, Health and Social Affairs on Northrhine-Westphalia are reported.

Vinyl Chloride Mortality Study

The aims of this study were to determine standardized mortality ratios (SMR) for male workers exposed to VCM, using the mortality rates of the West German male population as reference, to study the SMRs of a cohort of workers of the chemical industry comparable concerning age distribution and observation period but not exposed to VCM and to determine the SMR of a cohort of workers in PVC-processing plants.

The study was designed as a historic cohort study, covering the period from the beginning of the VCM- and PVC-production in all of the German plants till the end of 1974.

Table 1 shows the main characteristics of the three cohorts investigated. Only Germans and Austrians were included in data analysis because of insufficient mortality data on various foreign nationals employed in German factories. To determine the mortality rates of Austrians, West German rates were used. To calculate expectations of total mortality, the mortality rates of the adequate years have been used. To calculate expectations of specific causes of death for all years before 1968, the rates of 1968 have been used; for the following years the rates of the corresponding years. Following the procedure applied by Tabershaw (*1*), weighting of observed cases of specific causes of death according to unknown causes of death has been done with weighting factors calculated separately for three observation periods (up to 1959, 1960-1969, 1970-1974) as well as for six age groups.

In all of the cohorts, follow-up rates have been near or above 90%. The percentage of causes of death that could not be investigated due to loss or deletion of death certificates varied from 7.3% to 13.1%. To calculate age-standardized mortality ratios of specific causes of death, weighting has been done according to the procedure used by Tabershaw and Gaffey (*1*) to compensate for unknown or unidentified causes of death.

Table 2 displays total mortality as well as some of the relevant specific causes of death. It can be observed that the otherwise observed "healthy worker effect" cannot be demonstrated in the German cohorts exposed to VCM or employed in PVC-processing plants.

In the VCM cohort there are significant elevations of SMR of malignancies of the lymphatic and hematopoietic tissues (ICM 200-209), and of malignancies of the GI tract (ICD 150-159). The latter is due to the paramount elevation of SMR of tumors of the liver (ICD 155).

It must be noted that there is a modest elevation of SMR of tumors of the liver also in the cohort not exposed to VCM nor employed in PVC-processing plants. No obvious explanation for this observation can be offered. In addition elevated SMRs for ischemic heart disease (ICD 410-414) can be found in all of the three cohorts. Due to methodological

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shortcomings of the study no assessment of cardiovascular risk factors has been made. Therefore these results are of minor interest.

When subdividing the VCM-exposed cohort according to time of exposure there is a clear-cut increase of the SMR of liver tumors with time (Table 3). This seems to be highly suggestive of a time-response pattern. As it has been impossible to determine concentrations of VCM retrospectively due to technological and methodological problems no dose-response pattern can be established. However time of exposure seems to be the best available guess for dose.

Subclassification according to observation period

Table 1. Characteristics of study cohorts.

	Group I, VCM/PVC production	Group II, reference group	Group III, PVC processing
Population (Germans + Austrians)	7.021	4.910	4.007
Man years	73.734	76.029	52.896
Follow-up completed till 12/31/74, % deceased	98.2	89.8	92.1
Observed	414	417	360
Expected	435	533	380
Unknown causes of death			
No.	30	47	47
%	7.3	11.3	13.1
Total mortality (SMR)	95	78	95
Foreigners (excluding Austrians)	882	711	1.454
Deceased	6	6	10

Table 2. Standardized mortality ratios.

		VCM/PVC production		Reference group		PVC processing	
ICD 8	Cause of death	Obs.	SMR	Obs.	SMR	Obs.	SMR
Total mortality		414	95	417	78	360	95
140–209	All malignant tumors	94	112	83	83	62	85
140–199	Malignant tumors of organs	79	108	77	83	60	89
200–209	Malignancies of lymphatic and hematopoetic tissues	15	214[b]	6	77	2	34
150–159	Malignant tumors of GI tract and peritoneum	45	149[a]	27	71	15	56
155	Malignant tumors of the liver	12	1523[b]	4	401[a]	3	434
191	Malignant tumors of the brain	2	162	2	184	5	535[a]
400–414	Ischemic heart disease	91	127[a]	115	131[a]	96	156[b]
410	Acute myocardial	66	114	83	120	69	143[a]
800–949	Accidents	61	137[a]	44	99	32	110

[a]Beyond 95% confidence interval (2).
[b]Beyond 99% confidence interval (2).

Table 3. Standardized mortality ratios by duration of exposure.

		Duration of exposure, months							
		< 12		13–16		61–120		> 121	
ICD 8	Cause of death	Obs.	SMR	Obs.	SMR	Obs.	SMR	Obs.	SMR
Total mortality		53	98	138	102	98	87	130	96
140–199	Malignant tumors of organs	6	74	20	88	22	116	31	115
200–209	Malignancies of lymphatic and hematopoetic tissues	1	92	4	186	5	287	5	249
150–159	Malignant tumors of GI tract and peritoneum	3	101	12	135	13	173	17	156
155	Malignant tumors of the liver	0	–	2	874[a]	3	1525[b]	7	2528[b]
191	Malignant tumors of the brain	0	–	0	–	1	350	1	278

Table 4. Standardized mortality ratios by period of observation.

ICD 8	Cause of death	Observation period: To 1959 Obs.	To 1959 SMR	1960–69 Obs.	1960–69 SMR	1970–74 Obs.	1970–74 SMR	Total Obs.	Total SMR
140–199	Malignant tumors	12	160	29	84	194	103	414	95
200–209	Malignancies of lymphatic and hematopoetic tissues	1	147	9	275[b]	5	168	15	214[b]
150–159	Malignant tumors of GI tract and peritoneum	8	270[a]	13	94	24	177[b]	45	149[a]
155	Malignant tumors of the liver	1	1282	3	634[a]	8	2264[b]	12	1523[b]
191	Malignant tumors of the brain	1	557	0	–	1	223	2	162

[a]Beyond 95% confidence interval.
[b]Beyond 99% confidence interval.

Table 5. Standardized mortality ratios by age.

ICD 8	Cause of death	Age group: ≤ 24 Obs.	≤ 24 SMR	25–34 Obs.	25–34 SMR	35–44 Obs.	35–44 SMR	45–54 Obs.	45–54 SMR	55–64 Obs.	55–64 SMR	≥ 65 Obs.	≥ 65 SMR	Total Obs.	Total SMR
Total mortality		10	68	45	111	65	104	90	101	106	80	90	103	414	95
140–199	Malignant tumors of organs[b]	0	–	4	141	13	188[a]	19	141	22	76	21	100	79	103
200–209	Malignancies of lymphatic and hematopoetic tissues	0	–	2	194	4	303	4	264	3	162	2	197	15	214[b]
150–159	Malignant tumors of GI tract and peritoneum	0	–	3	397	10	365[b]	10	145	10	89	12	140	45	149[b]
155	Malignant tumors of the liver	0	–	0	–	6	6865[b]	0	–	3	934[b]	3	1664[b]	12	1523[b]
191	Malignant tumors of the brain	0	–	0	–	0	–	1	254	1	362	0	–	2	162

[a]Beyond 95% confidence interval.
[b]Beyond 99% confidence interval.

Table 6. Groups for subdivision of laboratory examinations.

Group	Specification
A-I	VCM/PVC production
A-II	PVC processing
B-I	VCM/PVC production and PVC processing, work capacity loss < 20%
B-II	VCM/PVC production and PVC processing, work capacity loss ≥ 20%
C-I	Germans and Austrians
C-II	Foreigners (Excl. Austrians)
D-I	Plants with high morbidity
D-II	Plants with low morbidity

Table 7. Bromsulfalein retention.[a]

	VCM/PVC Production	PVC Processing	Total
Retention normal	26	21	47
Retention abnormal	44	10	54
Total	70	31	101

[a]Chi square$_1$ = 8.09 ($p < 1\%$).

Table 8. Bromsulfalein retention.[a]

	Germans and Austrians	Foreigners	Total
Retention normal	17	30	47
Retention abnormal	33	21	55
Total	50	51	101

[a]Chi square$_1$ = 6.25 ($p < 2.5\%$).

Table 9. Bromsulfalein retention.[a]

	Work capacity loss < 20%	Work capacity loss > 20%	Total
Retention normal	41	6	47
Retention abnormal	32	22	54
Total	73	28	101

[a]Chi square$_1$ = 9.81 ($p < 1\%$).

(Table 4) reveals a rather inconsistent pattern: malignancies of the lymphatic tissues (ICD 200-209) are significantly elevated in the sixties only, whereas SMRs for tumors of the liver increase till the end of the study period. This might be referred to different latency periods for both kinds of malignancies, but other causes might likewise have contributed to these results. However, it has to be reported that the number of angiosarcomas confirmed histologically in the Federal Republic of Germany in patients previously exposed to VCM has actually come to 17 in contrast to mere 4 at the endpoint of the mortality study (12/31/1974).

The distribution of SMRs by age (Table 5) demonstrates an obvious susceptibility of males aged 35-44 for malignancies in general as well as for malignancies of the liver.

The data base for the German morbidity study consists of all of the reports of suspected cases of occupational disease due to VCM or PVC production or PVC processing. The reference population for these reports has to be defined as the total

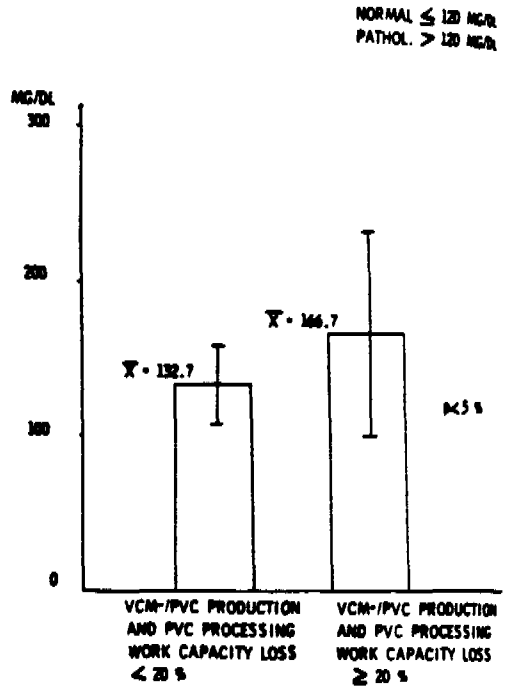

FIGURE 2. Vinyl chloride morbidity study: oral glucose tolerance test, 120 min after loading (normal 120 mg/dl).

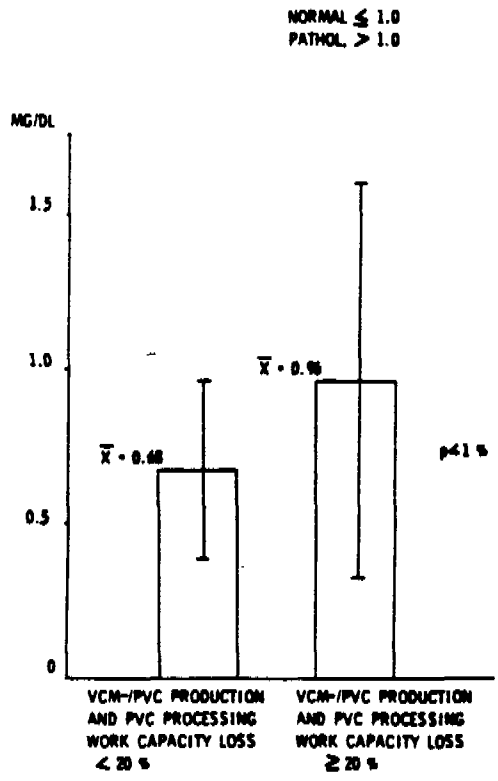

FIGURE 1. Vinyl chloride morbidity study: total bilirubin (normal 1.0).

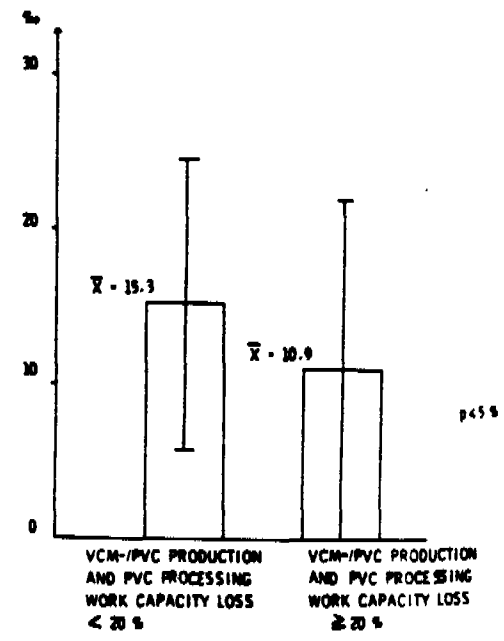

FIGURE 3. Vinyl chloride morbidity study: reticulocytes (normal 15‰).

working population in 1974 in the above mentioned branches, i.e., 6,500 workers in VCM or PVC production and 42,800 workers in PVC processing as given by the German Association of Plastic Producing Industries). Till the end of 1974, 269 reports of suspected cases of occupational disease had been received. As there has been no consistent set of examinations performed on each of the cases, numbers of observations for various variables analyzed vary according to examination method performed. Insofar as the results of this study are of much lower validity than those of the mortality study, one should regard them as hints for further investigations.

Four attempts to subclassify observation on the 269 cases have been undertaken (Table 6). Only those results showing significant differences when applying *t*-tests or chi-square tests are so classified. Amazingly none of the more sensitive lab examinations of liver functions showed a marked difference in all of the subclassifications besides bromsulfalein retention. In this instance there is a significant difference when subdividing by VCM/PVC production versus processing (Table 7), as well as by nationality (Table 8) and most pronounced when subdividing by extent of work capacity loss (Table 9). This latter result, however, must be expected when an effect of exposure on liver function is anticipated. An impairment of the excretory liver function is suggested by elevated total bilirubin values in the subgroup with work capacity loss greater than 20% (Fig. 1). There seems to be an impaired glucose tolerance in this group, although observed in a small subsample only (Fig. 2), as well as a lower number of reticulocytes (Fig. 3). The thromocyte count in both groups was the same. These results, however, lead to no sensible interpretation, as all results attempts failed to standardize the methods applied for thrombocyte counts by various laboratories.

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Epidemiologic Study of Vinyl Chloride Workers: Mortality through December 31, 1972

by W. Clark Cooper*

A population of 10,173 men, employed in 37 plants, was identified as having worked for at least one year in jobs involving probable exposure to vinyl chloride monomer (VCM) prior to January 1, 1973. Of the 9677 men whose vital status was determined, 707 were known to have died. For 699, death certificates were obtained. The standardized mortality ratio (SMR) for all causes was 89, that for all malignancies was 104. The only type of malignancy found in significant excess was in the category of malignant neoplasms of the brain and other parts of the nervous system; 12 deaths occurred where 5.9 were expected, for an adjusted SMR of 203. There were slight but inconclusive upward trends in all malignancies, and for malignancies of the respiratory tract, digestive tract, and central nervous system associated with reported levels of maximum exposure to VCM. When groups in whom less than 20 years had elapsed from the first exposure were compared with those with 20 or more elapsed years, and 25 or more elapsed years, no significantly different SMR's were detected for major primary sites of malignancy. Plans for an updated study of mortality, to include deaths in the period 1973–1979 are briefly discussed.

The epidemiologic studies of vinyl chloride workers summarized in this report were carried out during the period June 15, 1973 through December, 1976 by Tabershaw-Cooper Associates, Inc., and Equitable Environmental Health, Inc., for the Manufacturing Chemists Association (MCA) (now the Chemical Manufacturers Association).

An initial report, dealing with 8,384 workers from 34 plants, was prepared May 3, 1974 (*1*). A summarized version (*2*) was published in 1974. The study population was subsequently increased and follow-up was improved. After an interim report in 1976 (*3*), a final report based on 10,178 workers was prepared in January, 1978 (*4*). In all of these studies the observation period ended December 31, 1972.

Participating Plants

In mid-1973, the MCA identified 43 plants in the United States, belonging to 19 companies, which either produced vinyl chloride monomer (VCM) or used it in the production of poly(vinyl chloride) (PVC). Of these, 34 were included in the initial study; four were excluded because they had been in operation less than 5 years, one had stopped production in 1966, and in others information on job histories or exposures was deficient. Three plants were subsequently added to the original 34, so the 1978 report included 37 plants. Of these, 11 produced only VCM, 18 produced only PVC, three produced both, and five plants produced homopolymers and copolymers, with or without VCM and PVC.

The geographical distribution of those in the study, as shown in Table 1, indicates a disproportionate number of workers from the South, particu-

Table 1. Geographical distribution of 10,173 vinyl chloride workers in 1978 report.

Region	U.S. males (1970), %	Workers in study, %
Northeast	23.8	25.9
North Central	27.9	18.4
South	30.9	64.8
West	17.4	0.9

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larly from the East South Central and West South Central States. The South, with 30.9% of the total U.S. male population in 1970, supplied 64.8% of the study population.

Of the plants participating, the one which had first begun operations with VCM had done so in 1935, the most recent was in 1968. Four plants had begun in 1942 or earlier, 13 in 1952 or earlier, and 27 in 1962 or earlier.

The Study Population

The objective was to include all male employees whose work had involved exposure to vinyl chloride for at least one year prior to December 31, 1972. The designation of jobs which involved exposure to VCM was made by staff members at individual plants or by a corporate industrial hygienist. In approximately two thirds of the study population, TCA staff copied personnel records on individuals who were identified as having been in exposed jobs. In the remaining portion of the population, detailed information on exposed individuals was provided by plant personnel. The methods used in doing this are described in the complete reports cited earlier.

Study Period

The period of time in which the work-force of a plant was included in the study depended upon the date it began making or using VCM and also upon the earliest date when personnel records were complete for all employees, if that was later than the foregoing. This was done to eliminate periods when there was differential record retention of workers terminated, deceased, or retired. The end of the study period was December 31, 1972.

Estimates of Exposure

In each plant, every job and location with VCM exposure was graded in terms of probable exposure. Originally, a job history form was designed in the expectation that the exposures could be quantified in parts per million. This proved impossible in practice. However, for each plant, jobs and locations involving the highest exposures could be classified as "high", and other jobs classified as "medium" or "low" relative to the "high". It is recognized that this subjective classification is of questionable validity in categorizing the past and present exposure of a given worker. From the number of months spent in jobs with classifications of 3 (high), 2 (medium) and 1 (low), a number of exposure categories were developed for use in later analyses. As shown in Table 2, individual exposures in various papers were classified in a number of ways, including the maximum level at which an individual had been exposed for at least 12 months, an integrated or cumulative exposure, and an exposure index based on the cumulative score divided by the number of months.

Table 2. Bases for development of VCM exposure categories

Criterion	Unit
Duration of exposed employment	Months
Interval from beginning of exposure to end of observation	Months
Estimated maximum level to which an individual was exposed for at least 12 months, classified as high, medium, or low.	High Medium Low
Integrated or cumulative exposure, crediting 1 for each month at low, 2 for each month at medium and 3 for each month at high exposure to VCM	1 2 3
Exposure index (EI) = Cumulative score/average number of months	

Follow-Up

As is customary in historical prospective studies, all who had left employment were traced when possible. Methods included form letters sent by mail and use of retail credit follow-up. For the first report, there was insufficient time to utilize Social Security Administration records, but for subsequent reports such follow-up was used.

In the first, or 1974 report, 85% of the study population was located; for the final or 1978 report, the percentage had been increased to 95%.

The mortality calculations were based only on those who were successfully traced, which is equivalent to assuming that mortality among those not found was the same as among those who were found. This usually, but not always, results in some overestimation of mortality.

Calculation of Standardized Mortality Ratios

Each worker in the study, i.e., everyone whose vital status was ultimately known, was considered to have been under observation from the date on which he attained a year of exposed employment or from the date when his plant's records were complete, whichever came later. Observation periods ended December 31, 1972, or on the date of death, whichever occurred first.

Observed deaths were classified by cause according to the 7th (1955) revision of the International

Classification of Diseases. The expected number of deaths by cause were calculated by using age and cause-specific mortality rates for United States males with the same birth years and age distribution for the years 1950, 1955, 1959, 1965, 1967 and 1970.

Deaths for which death certificates could not be obtained were assumed to have the same cause distribution as the death certificates that were obtained. Appropriate increases were made in calculated SMR's.

The statistical significance of the deviation of each SMR in the study population from an expected value of 100 was tested by a method derived from Chin Leong Chiang (*5*). The formula for determining the standard error of the SMR was

$$SE = \sqrt{\frac{100 \times SMR}{\text{No. expected deaths}}}$$

If an observed SMR differed from 100 by more than 1.96 standard errors, it was regarded as significant at the 5% level; if it differed by more than 2.57 standard errors, it was regarded as significant at the 1% level. SMR's based on fewer than five observed deaths were usually not tested for significance.

Results

Table 3 summarizes the numbers of individuals, success of follow-up, person-years and deaths in successive phases of the study. The number of deaths per 1000 man-years of observation, which in general reflects the age distribution of the work force, suggests that the proportion of older individuals increased in the study population as it was expanded and follow-up improved. Even so, the 5.88 deaths per 1000 man-years indicates that a relatively young population was being observed; the U.S. male population 20 and above has about 11 deaths per 1000 man-years. Some published occupational epidemiologic studies will show 20 or more.

Table 3. Numbers of individuals, success of follow-up, person-years, and deaths analyzed in successive phases of the study.

	Report 1, 1974	Report 2, 1976	Report 3, 1978
No. of men	8,384	9,109	10,173
No. found	7,128	8,714	9,677
% found	85%	96%	95%
No. deaths	352	525	707
No. certificates	328	511	669
Total man-yr	77,846	94,221	120,203
Deaths/1000 man-yr	4.52	5.57	5.88

Duration of Exposure to VCM

In the first report, only 15.2% of those studied had begun exposure prior to 1950 (22 years before end of the observation period). In the third report, 33.4% had had 20 or more years for observation since exposure began. This resulted from finding more early employees by improved follow-up, and the inclusion of an older group from one plant in the augmented population.

Standardized Mortality Ratios

Standardized mortality ratios (SMR's) for selected causes of death are shown in Table 4, based on the 352 deaths analyzed in Report 1 and the 707 deaths analyzed in Report 3. Results in the first report led Tabershaw and Gaffey (*1*) to conclude that vinyl chloride may be associated with cancer of a number of sites, notably digestive cancer, respiratory cancer, cancer of other and unspecified sites (primarily those of the central nervous system) and lymphomas. This was based not on statistically significant excesses in each category, but upon apparent trends when different levels and durations of exposure were compared.

With the enlarged study group, the SMR for malignancies in the entire population dropped slightly, as did the SMR's for malignancies of the buccal cavity and pharynx, digestive tract and respiratory tract. However, tumors of the brain and central nervous system, when examined separately, still appeared to be in excess.

A number of analyses were done in the third report in an attempt to sharpen the focus on work exposures.

There appeared to be a slight but definite trend in the SMR's for all malignancies, malignancies of the digestive tract, the respiratory tract, and for other and unspecified sites with increasing levels of estimated maximum exposure (Table 5). However, the numbers of expected deaths were relatively few in some categories and the groups differed widely in age distribution as manifested by deaths per 1000 person-years.

To reduce dilution of the study population by men whose exposures had begun only recently, a separate analysis was carried out on those whose exposures to VCM had begun 20 years or more prior to 1972, and on those whose exposures had begun 25 years or more prior to 1972 (Table 6).

Another analysis was made of a population of men who had worked in plants producing only PVC

(where VCM exposures were presumably high), whose exposures had begun 20 years or more before the end of the study period and who had been reported as having medium or high VCM exposures for a year or more (Table 7). This group experienced 210 deaths where 249.7 had been expected. The pattern of mortality from malignancies was not appreciably different from that of the total study group.

In summary, increasing the study population and

Table 4. Observed and expected deaths (O/E) and standardized mortality ratios for selected causes (SMR's adjusted for missing death certificates).

Cause (ICD Mo, 7th Rev)	1974 Report		1978 Report	
	O/E	SMR	O/E	SMR
All causes	352/467	75[a]	707/795	89[a]
All malignancies (140–205)	79/77	110	139/141	104
Buccal and pharynx (140–148)	5/2.84	189	5/5.19	102
Digestive (150–159(	19/21.7	94	29/40.8	75
Respiratory (160–164)	45/44.3	112	25/23.9	107
Other and unspecified (190–199)	17/11.75	155	28/20.2	147
Brain and CNS (193)	—	—	12/5.9	203[b]
Leukemia and aleukemia (204)	3/3.77	85	9/6.65	143
Lymphomas (200–203, 205)	6/6.06	106	11/10.36	112
Major cardiovasc. renal (330–334, 400–468, 592–594)	155/207	80[a]	347/385	95
Cirrhosis liver (581)	3/15.6	21	14/26.5	56[b]
No. of workers	7,128		9,677	
Person-yr	77,846		120,203	

[a]Significant at 1% level.
[b]Significant at 5% level.

Table 5. Observed and expected deaths (O/E) and standardized mortality ratios for selected causes as related to maximum level of reported exposure to vinyl chloride monomer (SMR's adjusted for missing death certificates).

Cause (ICD Mo, 7th Rev)	Reported maximum exposure VCM					
	Low		Medium		High	
	O/E	SMR	O/E	SMR	O/E	SMR
All malignancies (140–205)	65/71	96	56/53.5	109	18/16.5	112
Digestive (150–159)	14/20.9	72	10/15.6	67	5/4.4	117
Respiratory (160–164)	19/22.2	92	19/17.1	116	7/5.1	141
Other and unspecified (190–199)	11/9.9	119	13/7.5	180	4/2.7	150
No. of workers	4,925		3,021		1,731	
Person-yr	58,741		39,927		21,535	
Deaths/1000 person-yr	6.16		6.6		3.9	

Table 6. Analysis of deaths based on time from beginning of exposure to end of study period (SMR's adjusted for missing death certificates).

Cause of death (ICD No. 7th revision)	< 20 yr		> 20 yr		> 25 yr	
	No.	SMR	No.	SMR	No.	SMR
All causes	156	77[a]	549	93	398	96
All malignancies (140–205)	31	95	108	107	73	104
Digestive (150–159)	8	96	21	70	16	74
Respiratory (160–164)	8	80	37	116	22	100
Other and unspecified (190–199)	6	108	22	162	13	146
Leukemia (204)	3	155	6	137	4	137
Cardiovascular-renal	68	84	279	97	211	105

[a]Significant at 1% level.

proving follow-up did not strengthen the suggested associations between VCM exposure and malignancies other than those caused by hepatic angiosarcoma, as will be pointed out later, and a suggested association with tumors of the brain and central nervous system.

Table 7. Deaths in plants producing only PVC, based on workers whose first exposures began before 1952, and who had medium or high VCM exposures (SMR's corrected for missing death certificates).

Cause of death (ICD No. 7th revision)	O/E	SMR
All causes	210/249.7	84[a]
All malignancies (140–205)	46/46.04	106
Digestive (150–159)	9/13.63	70
Respiratory (160–164)	17/14.75	122
Other and unspecified (190–199)	10/ 6.33	167
Cirrhosis of liver (581)	6/7.95	80

[a] Significant at 1% level.

Angiosarcomas

Nine angiosarcomas are known to have occurred in the U.S. during the study period, i.e., prior to 12/31/72. As shown in Table 8, eight of these were found in the study, but only three were coded as angiosarcoma on the death certificate. However, four others were coded as tumors of the digestive tract. Unfortunately, two were coded 230x so as to fall out of the category for malignant tumors of the GI tract, and one was coded as cirrhosis of the liver.

As shown in Table 8, the angiosarcoma which was not found was in a man who had died in 1961. We have not determined how he failed to be in the study population. The years of exposure for the eight cases ranged from 4 to 23 years, while elapsed time from beginning of exposure to death ranged from 16 to 24 years.

Tumors of the Central Nervous System

The 12 tumors of the brain had been diagnosed on death certificates as follows: glioblastoma multiforme, 4 (1 confirmed by autopsy); astrocytoma, 2 (2 au-

Table 8. Angiosarcoma deaths and data on VCM exposures.

ICI No.[a]	First exposed	Year of death	Time from first exposure to death, yr	Total yr exposure	Est. max. exposure	Age at death
USA-02	1955	1971	16	14	High	38
-04	1949	1968	19	18	High	43
-05	1944	1964	20	20	High	52
-07	1944	1968	24	14	Med	45
-10	1946	1970	24	23	Low	70
-11	1951	1968	17	17	Med	60
-12	1949	1969	20	20	High	50
-16	1950	1969	19	4	High	41
-06	—	1961		Not in study group		

[a] Number used in registry periodically prepared by J. Stafford, Imperial Chemical Industries Ltd., Plastics Division.

Table 9. Summary of brain tumor deaths (ICD No. 205) and data on VCM exposures.

Case no.	First exposed	Yr of death	Time from 1st exposure to death, yr	Total yr exposure	Max. exposure	Age at death
1	1958	1972	14	5	Low	67
2	1967	1972	5	5	Low	43
3	1957	1968	11	7	Med	54
4	1941	1958	17	6	Med	61
5	1950	1970	20	8	High	43
6	1956	1971	15	3	Med	54
7	1947	1971	24	23	Low	57
8	1945	1963	18	18	High	44
9	1949	1971	22	21	Low	58
10	1947	1971	24	23	High	49
11	1935	1956	21	18	Low	59
12	1935	1967	32	22	Low	57

topsies); ependymoma of the 4th ventricle (autopsy); "malignant brain tumor" or "carcinoma of the brain," 5 (with no autospies). This group is currently being made the subject of more rigorous review. The information obtainable from our records, summarized in Table 9, is insufficient to prove or disprove a cause-and-effect relationship between occupational exposure and these tumors.

Conclusions

A study of 707 deaths in a population of 9677 men who had worked for one year or more in jobs involving exposure to vinyl chloride and whose vital status had been determined as of December 31, 1972, did not show a significant excess of deaths due to malignancies. There did appear, however, to be a significant excess of tumors of the brain and central nervous system, based on 12 such deaths. There also continued to be slight but inconclusive trends toward higher SMR's for deaths from digestive tract and respiratory tract tumors associated with maximum levels of past exposure. No striking changes in malignancy patterns were apparent when analyses were directed toward individuals in whom 20 to 25 years had elapsed since first exposure. The results suggest that, except for a proven association with hepatic angiosarcoma and a strongly suggestive association with central nervous system tumors, vinyl chloride probably is not associated with significant excess cancers of other sites.

It should be emphasized that the epidemiologic study summarized in this report was planned, the populations defined, and analysis under way before cases of hepatic angiosarcoma had been diagnosed in workers exposed to vinyl chloride (*6*). An update is scheduled with inclusion of additional deaths in the cohort during the years 1973 through 1979. The study can be improved by a separate analysis of data from the plants which began operations before 1960, and by separating, insofar as possible, exposures to vinyl chloride monomer, polyvinyl chloride, and various copolymers. It is also hoped that criteria for defining exposure and for rating levels of exposure can be improved to permit better indices of integrated exposure.

This study was begun June 15, 1973 under a contract between the Manufacturing Chemists Association, 1825 Connecticut Avenue, N.W., Washington, D.C. (now the Chemical Manufacturers Association) and Tabershaw/Cooper Associates, Inc. It was continued under later contracts with TCA and with Equitable Environmental Health, Inc.

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Epidemiology of Hepatic Angiosarcoma in the United States: 1964-1974

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A nationwide survey of hepatic angiosarcoma (HAS) in the United States during the years 1964 through 1974 identified 168 cases. Of these, 42 cases (25%) were associated with known etiologic factors, such as vinyl chloride monomer exposure during preparation of poly(vinyl chloride), use of Thorotrast in angiography, exposure to inorganic arsenic, and treatment with androgenic-anabolic steroids; 126 cases (75%) are of uncertain etiology. HAS most often affects males (ratio of approximately 3:1), peaks in the sixth and seventh decades of life (somewhat earlier than other sarcomas of the liver) and appears to occur more often in the industrialized Northeast and Midwest (although reporting artifact may be a factor). There is an extraordinary relative risk for poly(vinyl chloride) polymerization workers; there may also be other chemical-industrial associations that require further investigation. Prospective epidemiologic studies of HAS should be considered as a means of identifying other causative factors (e.g., chemicals or drugs) related to HAS.

Introduction

This report is an overview of the nationwide hepatic angiosarcoma (HAS) case-finding study for the years 1964-1974 conducted by the Centers for Disease Control (CDC).

At the start of this study, three causative factors had been identified for HAS: vinyl chloride monomer (VCM) (*1*, *2*), Thorotrast (*3*), and inorganic arsenic (*4*). The recently discovered association between VCM and HAS has served as a stimulus for this investigation, and multiple epidemiologic studies of polyvinyl chloride (PVC) polymerization workers exposed to VCM have since demonstrated very high relative risks for the development of HAS (*5*, *6*). Thorotrast is a colloidal suspension of thorium dioxide, a radioactive alpha-emitter with markedly prolonged radiologic and biologic half-lives, which was used for carotid angiography and liver-spleen scans in the period 1930-1955. The thorium dioxide is sequestered by the reticuloendothelial system, primarily in the Kupffer cells of the liver; radiation injury to adjacent cells is the presumed carcinogenic mechanism. Epidemiologic studies of Thorotrast recipients have shown very high relative risks for the development of HAS as well as hepatocellular tumors (*7*, *8*). The association between arsenic and HAS is based on data from several small autopsy series in German vintners in the 1940s and 1950s (*4*, *9*), which demonstrated an increased incidence of liver disease, including HAS. These workers were exposed to inorganic arsenical pesticides during application of the pesticide and also by drinking beverages prepared from the skins of the sprayed grapes. Subsequently, HAS cases were reported following long-term ingestion of Fowler's solution (potassium arsenite) (*10*, *11*) and

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arsenic-contaminated well water (*12*). Individual cases suggesting associations between HAS and hemochromatosis (*13*) and copper exposure (*14*) have also been reported.

Earlier reports from this study reviewed cases associated with single causative factors (*15-18*), including androgenic-anabolic steroids which we feel are implicated as a fourth cause of HAS (*19*). In this paper, we present an overview of the case-finding effort, placing the known causative factors and cases of idiopathic origin in perspective.

Methods

Information relating to cases of HAS occurring in the United States during the years 1964 through 1974 was solicited by CDC in a variety of ways: (1) announcements were placed in seven medical journals; (2) a mailing was sent to all pathologists in the country; (3) separate mailings were sent to all state epidemiologists, major tumor referral centers, and statewide tumor registries; (4) a death certificate review for International Classification of Diseases (ICD), Eighth Revision, Code 197.8 (liver tumors, unspecified primary or secondary) for the period 1966-1973 was conducted with the assistance of the National Center for Health Statistics (NCHS) and the 50 state health departments (Code 155.0, primary liver tumors, was not reviewed because it would have been impractical to obtain the much larger number of certificates in this category and because it was felt that the majority of cases of HAS listed as such on the death certificate would have been coded as 197.8); (5) arrangements were made with the Armed Forces Institute of Pathology (AFIP) to include cases in their files (1943-1975) in the review; (6) a number of cases were identified from industrial surveys of PVC polymerization workers and others potentially exposed to VCM; and (7) permission was requested to include the previously published cases of HAS occurring in 1964-1974.

The evaluation procedure for each identified case was as follows: Initially, permission was requested to review the appropriate pathologic specimens (all submitted non-AFIP case material was reviewed at the National Cancer Institute's Laboratory of Pathology by H. P. and L. B. T.). Following confirmation of the diagnosis, the local physician was notified, and, with his permission, the nearest of kin was identified and contacted. Consent was obtained to review medical records, and a questionnaire was administered by telephone to obtain detailed occupational, residential, and chemical exposure histories. In selected instances, friends, employers, previous physicians or others were also interviewed.

In all, approximately 350 submitted cases were reviewed by the pathology review group, some outside our requested time period of 1964-1974. Pathologic specimens were obtained for review in approximately 95% of cases, many of which were considered by our pathology panel not to be HAS. Since survival after diagnosis is very brief and many cases were only diagnosed at autopsy, we have included all 168 confirmed cases with death during 1964-1974 in the study group.

The above effort is essentially a case review. Subsequently, the 22,432 death certificates obtained from the review of Code 197.8 were used to carry out a case-control study of occupation as recorded on the death certificate in the following manner. Death certificates were sought for all 168 confirmed HAS cases; 166 were available. Controls were sought from among the 22,432 death certificates in ICD Eighth Revision Code 197.8 (liver tumor, unspecified primary or secondary) that had been obtained in the HAS case-finding effort (see above). certificates of confirmed HAS cases were excluded from the control selection process. Although deaths in Code 197.8 might not represent the ideal control group, the rationale was that these deaths resulted from a broad variety of tumors of multiple sites metastatic to the liver or represented cases which were diagnostically uncertain; it was therefore unlikely that any single diagnostic category would predominate or that the occupational listings would be heavily biased by any single group of cases.

Up to four controls (as many as were available) were matched to each case ≥ 30 years of age on the basis of the following criteria: age (±6 years), sex, race, county of residence, and year of death (±3 years). One hundred thirty-five cases were successfully matched (79 of these had 4 matched controls; the overall ratio of controls to cases was approximately 3:1). Individuals who could not be matched were primarily young females and residents of sparsely populated counties.

A combined occupation and industry coding scheme was developed to accommodate all listings recorded on the certificates and to group listings on the basis of potential hazardous exposures. The data were analyzed by Rothman's method for matched groups with multiple controls per case (*20*).

Results

Our study identified 168 deaths from confirmed HAS during the years 1964 through 1974. For this rare tumor, the best sources of case identification were the pathologists, with the largest number of cases identified through the single mailing to all pathologists and the second largest number of cases

identified through pathology referral centers (particularly the AFIP).

Table 1 summarizes the results of the death certificate review portion of the case-finding effort and points up some of the inadequacies of using this method in epidemiologic studies of uncommon tumors. Only 42% of the cases initially identified on the death certificate as HAS were confirmed as such on pathologic review; 50% of the cases were confirmed not to be HAS. Furthermore, only 23% of all the total cases in our study during the years 1966-1973 would have been identified by the death certificate search alone. It can be seen that an epidemiologic study based only on a death certificate search of Code 197.8 would have been quite inadequate.

Figure 1 compares age, race and sex data for the confirmed HAS cases in our study with 131 cases of non-angio hepatic sarcoma identified in the death certificate survey (these latter cases were not confirmed by pathologic review). HAS has a striking male preponderance of approximately 3:1; this is not true for other hepatic sarcomas. HAS also appears to occur more often in younger age groups.

The higher proportion of males than females with HAS first appears in the 40- to 49-year-old group (Fig. 2) and is associated with a younger peak age for males than females, although the mean age for female HAS cases (50.1 years) is lower than that for males (57.9 years). These findings are not solely related to the VCM-induced cases among polymerization workers. The male preponderance is also present in the Thorotrast, arsenic, and androgenic-anabolic steroid associated cases, as well as in the idiopathic cases (Table 2). Cases with known etiology, however, have a younger age distribution than idiopathic cases (Table 3), with a mean age of 51.0 years compared to 57.6 years for the idiopathic cases.

Table 4 presents the 168 cases of HAS by year of death and etiologic status. The VCM-, Thorotrast- and androgenic-anabolic steroid-associated cases were more common during the latter part of the study

Table 1. HAS cases, CDC survey: death certificate review—code 197.8 (8th revision ICD), 1966–1973

Length of review	
7.5 years (1966–1971, 1973, 1/2 of 1972)	
Total number of death certificates reviewed	22,432
Sarcomas of the liver, death certificate diagnoses:	
Angiosarcoma (HAS)	74 (36.1%)
Leiomyosarcoma	24 (11.7%)
Fibrosarcoma	14 (6.8%)
Sarcoma (type unspecified)	64 (31.2%)
Sarcoma (other types)	29 (14.1%)
Total	205
Final pathologic diagnoses of 74 cases identified on death certificate as HAS	
Confirmed HAS	31 (42%)
Confirmed not HAS	37 (50%)
No pathology available	6 (8%)

Table 2. HAS cases, CDC survey, 1964–1974: sex ratios, etiologic categories.

	Male	Female	Ratio
Vinyl chloride	12	0	(12 : 0)
Thorotrast	15	5	(3 : 1)
Arsenic	4	2	(2 : 1)
Androgenic-anabolic steroids	3	1	(3 : 1)
Subtotal	34	8	(4.3: 1)
Idiopathic	93	33	(2.8: 1)

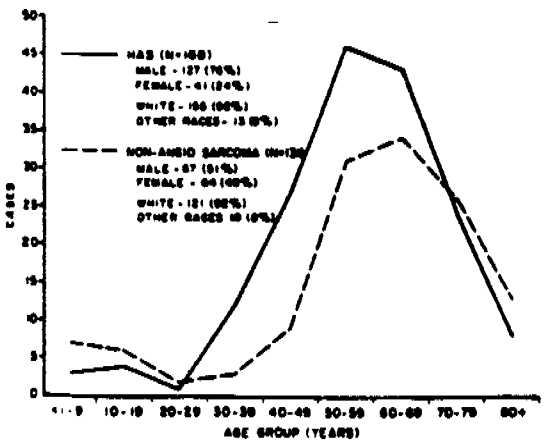

FIGURE 1. Hepatic angiosarcoma (HAS) cases compared with non-angio hepatic sarcoma cases, by age group: U.S., 1964-1974.

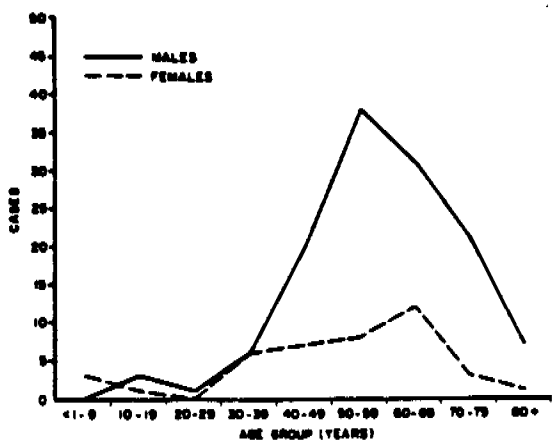

FIGURE 2. Hepatic angiosarcoma cases, by age group and sex: U.S., 1964-1974

Table 3. HAS cases, CDC survey, 1964–1974: age distribution for cases of known cause and for idiopathic cases.

Age, yr	Known etiology No. %	Idiopathic No. %
0–9	1 (2)	2 (2)
10–19	0 (–)	4 (3)
20–29	0 (–)	1 (1)
30–39	4 (10)	8 (6)
40–49	8 (19)	19 (15)
50–59	22 (52)	24 (19)
60–69	4 (10)	39 (31)
70–79	3 (7)	21 (17)
≥80	0 (–)	8 (6)
Total	42	126

period. For the VCM- and androgenic-anabolic steroid-associated cases, this is due to the relatively recent introduction of these causative agents. For the Thorotrast-induced cases, however, this pattern was an unexpected finding. Based on the originally calculated latent period of approximately 20 years (*21*), the general impression was that such cases would be diminishing by 1975. However, the number of cases appeared to still be increasing as of 1974, apparently due to an increase in cases having relatively low-dose angiographic procedures and prolonged latent periods (*16*). The arsenic-associated cases (including five adults with a history of prolonged use of Fowler's solution and one child with environmental exposure) occurred primarily during the earlier years of the study and may represent the tail end of a larger problem in previous years. The number of idiopathic cases was low during the first few years of the study (perhaps related to poor recall by pathologists, and to the fact that the death certificate search started with 1966). Case numbers, however, remained steady for most of the study period except for a spurt in 1974. The latter occurred right after the original report and the attendant publicity of the first cases of VCM-induced HAS (January 1974) and may be related to improved diagnostic evaluation. Review of the idiopathic cases occurring in 1974 demonstrated a large number of elderly cases with no evidence of clustering in a particular exposure setting.

The HAS mortality rate for the entire United States during the study period was 0.75 cases per 10^7 population per year. Crude mortality rates by region, based on county of residence at time of diagnosis (Table 5), suggest a somewhat higher incidence in the Northeast and in the industrial portions of the Midwest. There was also an increase in the mountain region, although this is based on a very small number of cases. The rates were low in farming states and in the South; however, since

Table 4. HAS cases, CDC survey, 1964–1974: distribution by causative factors and year of death.

	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974	Total
Idiopathic	4	10	9	13	12	13	11	12	13	11	18	126
Vinyl chloride	1	–	–	–	3	2	1	1	–	3	1	12
Arsenic	1	–	1	2	1	–	–	–	–	1	–	6
Thorotrast	–	–	–	1	2	2	3	2	4	1	5	20
Androgenic-anabolic steroids	–	–	–	1	–	–	–	1	–	1	1	4
Total	6	10	10	17	18	17	15	16	17	17	25	168

Table 5. HAS cases, CDC survey, 1964–1974: distribution by region.

Region	States	Pop. 1970	No. of cases (HAS/10^7/yr.)	No. of idiopathic cases (idiopathic HAS/10^7/yr.)
1. New England	ME, NH, VT, MA, RI, CT	11,847,186	12 (0.92)	9 (0.69)
2. Mid-Alantic	NY, NJ, PA	37,152,813	38 (0.98)	28 (0.69)
3. E.N. Central	OH, IN, IL, MI, WI	40,252,678	35 (0.79)	30 (0.68)
4. W.N. Central	MN, LA, MO, ND, SD, NB, KS	16,324,389	10 (0.56)	9 (0.50)
5. S. Atlantic	DE, MD, DC, VA, WV, NC, SC, GA, FL	30,671,337	23 (0.68)	15 (0.44)
6. E.S. Central	KY, TN, AL, MS	12,804,552	7 (0.50)	1 (0.07)
7. W.S. Central	AR, LA, OK, TX	19,322,458	12 (0.56)	10 (0.47)
8. Mountain	MT, ID, WY, CO, NM, AZ, UT, NV	8,283,585	10 (1.10)	7 (0.77)
9. Pacific	WA, OR, CA, AK, HI	26,525,744	21 (0.72)	17 (0.58)
Total		203,184,742	168 (0.75)	126 (0.56)

cases are diagnosed only after referral to hospital and tumor centers, it is possible that rural rates could be artifactual.

To summarize this portion of the study, it is apparent that HAS has a strong male preponderance, that it appears to occur more often in younger age groups than other sarcomas of the liver, and that there may be geographic differences which are unrelated simply to the distribution of VCM associated cases (the largest number of which were in Kentucky and West Virginia). As part of the follow-up effort we looked at occupation in the death certificate case-control study. Table 6 shows that the case-control ratios were elevated only for the last two occupational categories. The first of these (#7) shows a highly significant difference for chemical workers that is entirely related to exposure to VCM: all 10 cases were PVC polymerization workers. The last category (#8) combined a large number of laboring groups with potential exposure to a variety of chemicals; included are laborers, machinists, maintenance workers and others. The association of this heterogeneous grouping of occupations with HAS is not statistically significant, nor in reviewing the individual occupational data from the interviews with family members were we able to identify a specific chemical, plant, or process as a causative factor. Nevertheless, taken together with the earlier findings, this association suggests that some chemical exposure or industrial factors may be related to a portion of the idiopathic cases. Such an association would not be unreasonable; machinists, e.g., are potentially exposed to trichloroethylene (an experimental hepatocarcinogen that is structurally related to vinyl chloride), inorganic arsenic and nitrosamines (which have been identified in cutting fluids and are a known cause of HAS in animals) (*22, 23*).

Discussion

A particularly intriguing feature of HAS is that there are now four probable causes of this tumor, and yet about 75% of the cases are of uncertain etiology. Given that the HAS cases associated with the four quite distinct etiologic factors (VCM, Thorotrast, arsenic, and androgenic-anabolic steroids) share a common morphologic progression to HAS which is indistinguishable from that of idiopathic cases (*24*), it is likely that additional causal factors are (or will be) associated with HAS. In this study, the male preponderance, the younger age distribution, the possible geographic relationship with industrial portions of the country, and the suggestion from the death certificate case-control study that groups with chemical exposure may be at higher risk, raise the possibility that some of the idiopathic cases may be related to presently unidentified environmental or occupational exposures.

This study and that of Baxter et al. (*25*) confirm the limited diagnostic reliability of death certificate diagnosis of HAS and the need to assess a variety of

Table 6. Occupation as recorded on death certificate, case-control study, CDC HAS survey, 1964–1974.

Occupation	Cases (N - 135)	Control (N = 421)
Professional, technical, engineers	16	40
Managers, administrators	5	23
Sales, wholesale/retail trade	3	29
Clerical	9	13
Communications	1	5
Finance, insurance, real estate	2	4
Business, store owners, proprietors	5	11
Service workers	8	36
Housewife, homemaker	18	58
Military, government	2	3
Unlisted, retired, disabled	5	12
	74 (55%)	234 (56%)
Agricultural (farming, stock, feed, fisherman)	4 (3%)	23 (5%)
Mining	1 (1%)	8 (2%)
Transport	4 (3%)	21 (5%)
Carpenters, craftsmen	2 (1%)	9 (2%)
Manufacturing (unspecified, untitled, other)	2	13
Lumber, logging, wood products	0	3
Metal, steel	0	5
Food, beverages, tobacco, packing	2	6
Textiles	3	9
Paper, printing	1	5
Rubber/plastics	1	2
Automobile	0	3
	9 (7%)	46 (11%)
Chemical	10 (7%)	1 (0%)
		$p = 4.29 \times 10^{-7}$[a]
Machinist-metal cutter	7	14
Machine operators	0	8
Forgers, molders, casters	1	3
Painters	1	4
Sanitation, water works, power	3	2
Maintenance, custodians	5	9
Laborers	8	20
Construction	1	2
Heavy equipment operators	2	6
Repair services	1	5
Mechanics	2	6
	31 (23%)	79 (19%)
		$p = 0.11$[a]

[a]Statistical analysis for case-control study with multiple matches (*20*).

sources of data in order to identify cases for studies of rare tumors such as HAS.

The Thorotrast data are instructive because the initial estimate of the latency period has lengthened with time; recent cases have been in individuals who had relatively low-dose procedures but prolonged latent periods (*16*). This accentuates the need to continue evaluation of VCM exposed groups for the possible appearance of a similar pattern. The time frame covered by our study is perhaps too early to detect a sizable number of cases with relatively low VCM exposure either in occupational or environmental settings. In addition, Thorotrast-induced HAS was noted approximately 10 years before Thorotrast-induced hepatocellular tumors were recognized; given the identical morphologic appearance after VCM exposure, involving mixed hyperplasia of sinusoidal cells and hepatocytes, and the occurrence of hepatocellular tumors in experimental animals exposed to VCM (*26*), we need to continue to follow-up VCM-exposed cohorts for the possible appearance of hepatocellular tumors.

Cases of HAS associated with various factors have previously been reported (*14*, *27*, *28*); individual cases associated with hemochromatosis, prior radiotherapy, chloroprene exposure and chemotherapy with urethane were also noted in this study, but we have not discussed them in detail here.

It would appear valuable to continue epidemiologic studies of this rare tumor. This might enable early detection of additional etiologic factors for this disease, such as the various structural analogs of vinyl chloride (e.g., vinyl bromide and vinylidene chloride) which have had industrial use. However, because of the difficulty and time involved in establishing adequate surveillance for rare tumors such as HAS or mesothelioma, it would be best to establish a single framework for studying a number of rare tumors or marker illnesses at once. One would then be able, e.g., to survey pathologists or other groups at a single time to obtain information on a variety of such conditions.

HAS is a rare tumor with at least four probable causes and undoubtedly others that have not yet been identified. Ascertainment of the range of causative agents for HAS, as well as for more common tumors, presents a challenge to epidemiologists.

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The British Hepatic Angiosarcoma Register

by Peter J. Baxter*

A register of British cases of primary hepatic angiosarcoma (HAS) was established in 1974 to monitor the occurrence of cases from 1963 onwards. Details of cases dying in 1963-77 have been obtained. Thirty-five cases were agreed as HAS by a panel of liver pathologists, and occupational and medical information was obtained in the majority of these. Two cases were attributable to VCM exposure, and eight others had received intra-arterial Thorotrast. In 1978-79, two more cases were confirmed in VCM polymerization workers.

Introduction

In 1974, the Health and Safety Executive embarked upon a mortality study of all workers in Great Britain who had been exposed to vinyl chloride in the manufacture of vinyl chloride (VCM) or poly(vinyl chloride) (PVC), and a register of British cases of primary hepatic angiosarcoma (HAS). The mortality study embraced over 7000 people, and an analysis of deaths up to the end of 1974 has been published (*1*). The main finding was four certified cases of liver cancer, two of which were histologically confirmed HAS. An update of this analysis has been postponed while, with the collaboration of the factories concerned, exposure data are being refined to take into account job changes and exposure to PVC dust. A mortality study of PVC fabricators was considered, but remains in the planning stage. The register is also the basis for a case-control study of occupation for those cases occurring from 1974 onwards (*2*).

To determine the annual occurrence of HAS and to monitor its incidence, cases dying in 1963-73 were reviewed as well as those occurring after this period. Information on cases for the 15 years 1963-77 has now been obtained and will be outlined here. Further details may be found elsewhere (*3*, *4*).

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Methods

Cases were identified by a search of death certificates in seven appropriate categories of the International Classification of Diseases for a diagnosis of HAS (or one of its synonyms). Hospital pathologists and cancer registries were requested to report cases, as were the medical departments of factories manufacturing VCM or PVC. Some cases were identified from publications. When available, histological material was sought for all the reported cases and submitted to a panel of three liver pathologists (Drs. P. P. Anthony, R. N. M. MacSween and P. J. Scheuer), who reviewed the slides independently and without knowledge of the prior diagnoses. For control purposes, histological material from other liver cancers was included. For those cases agreed by the panel as HAS, the full medical records were sought and further information, for example, occupational histories and alcohol consumption, was obtained when possible by interview with the next of kin.

Results and Discussion

Eighty-eight cases were reported from all sources. The panel agreed the diagnosis in 32 cases and three more were agreed from among the controls. In half of the confirmed cases the diagnosis had been recorded on the death certificate, but the remainder would have been missed if reliance had been placed upon death certificates as the sole method of ascertainment. At least some clinical and

necropsy details were obtained in all but two patients. Occupational histories were obtained in 91%, the occupation recorded on the death certificate being accepted for the remainder.

The annual numbers of both reported cases and those agreed by the panel increased after 1975, so that in 1977, 12 cases were reported, 10 of which were agreed by the panel. Between 1968 and 1977 an average eight cases per annum were reported and three per annum were agreed by the panel, the population of Britain during this period being about 50 million. The observed increase in incidence was almost entirely due to 10 cases of known etiology; eight were patients who had received intra-arterial Thorotrast (a colloidal suspension of thorium dioxide), and two others had been VCM polymerization workers. Plotting on a map the last places of residence of all 35 agreed cases revealed a cluster of six Thorotrast cases in or around Edinburgh, where the use of Thorotrast in neurological diagnosis had been greater than at any other British center. One hundred and nine patients who had received intra-arterial Thorotrast in Edinburgh during 1933-48 have been followed up in detail (*5*): about three quarters of these patients have died, 13 (17%) from liver tumors. Histological material for review by the panel was available in nine of these. In those cases dying in earlier years, the tumors were predominantly cholangiocarcinomas, but later cases were all HAS, confirming that the recent emergence of Thorotrast-induced HAS in Britain is a real increase in incidence and not an artifact due to under-reporting of cases occurring in the past.

Twenty-eight of the 35 cases were males; one female infant died aged 8 months. For idiopathic cases, the male:female ratio was 4:1. Adult cases were assigned to one of the Registrar General's five social classes according to the occupation on the death certificates. The social class distribution was unremarkable, except that the only cases in social classes one and two were four men, all of whom were designated as electrical engineers. In fact, six out of the 28 males had worked in the electrical industry at some time, a figure in excess of any other industry. Three other men had been employed in workplaces where PVC was fabricated, but the occupational histories were inadequate to confirm that these men had worked with PVC. One other male case had lived for six years before his death within a half mile of a plant manufacturing PVC. Occupational exposure to arsenic did not appear to be a factor in any of these cases. Arsenical drugs were commonly prescribed in Britain in the past and, in a few areas, even until the early 1960's. However, one case only was suspected to have clinical evidence of chronic arsenical intoxication, but nail and hair analyses for arsenic were negative and the medical records were inadequate for verifying the use of arsenical drugs. None of these cases was recorded to have taken androgenic steroids (*6*), but one woman had taken an estrogen preparation for several years. Alcohol did not appear to be an important factor in the majority of cases, only four men having a history of heavy consumption.

In its age distribution, clinical presentation and prognosis, HAS resembled primary liver carcinoma (*4*). Upper abdominal pain and a hepatic mass were the commonest presentation, and extrahepatic metastases were found in 23% of cases only. Excluding the Thorotrast cases, and for men only, the median interval between the onset of symptoms and death was six months for those aged under sixty years, and only six weeks for those aged sixty and over, a difference which was statistically highly significant. Hemochromatosis was not evident in any of the cases.

In 1978-79, two more cases of HAS have been confirmed in polymerization workers, and another case has led to speculation that hydrazine derivatives, such as phenelzine, may induce angiosarcoma in man (*7*). It is too early to predict the full impact of past industrial exposure to VCM in Britain and at least until the picture becomes clearer the monitoring of HAS should continue.

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Effectiveness of Federally Required Medical Laboratory Screening in the Detection of Chemical Liver Injury

by Carlo H. Tamburro* and Richard Greenberg*

The increasing concern of industrialized societies over the potential health hazard of synthetic chemicals in the occupational environment has led to goverment requirements for medical laboratory screening of workers. The specific tests for such screening programs are most often selected on the basis of medical experience which utilized them in symptomatic or hospitalized populations. Required screening tests for hepatic injury including cancer in vinyl chloride workers has been systematically and prospectively studied in an industrial population working with synthetic rubber and plastics. Approximately 1300 employees were studied over a five-year period. A cohort of 969 male employees, for the purposes of analysis, were divided into a "standard" and "nonstandard" population based upon the absence or presence of significant medical disease (including liver disease). A subcohort of 120 individuals was further identified based on availability of liver biopsy. Evaluation of federally required studies included alkaline phosphatase (AP), γ-glutamyl transpeptidase (GGTP), alanine aminotransferase (ALT, SGPT), aspartic aminotransferase (AST, SGOT) and bilirubin (BR). Also studied were indocyanine green clearance (ICG) and radioisotopic liver spleen scans (L-S scans). The GGTP provided the highest positive predicted value as a screening test for identifying "nonstandard" individuals (individuals with all types of medical disease) followed by ICG, AST, ALT, L-S scan, AP, and BR.

In the identification of asymptomatic liver disease the GGTP had the least specificity due to a high false positive rate, while the AP provided the highest specificity. The ICG clearance however, provided the best combination of positive predictive value and sum of specificity and sensitivity. The AP provided additional increase in specificity as a follow-up study. There was no evidence that any of the other federally required tests added any additional benefit and did add significant increase in the false positive rate. These studies support the need for evaluating screening tests as to their sensitivity, specificity and positive predictive value, in asymptomatic individuals, before they are made established requirements.

Introduction

Industrialized societies throughout the world have become increasingly concerned over the potential health hazard of synthetic chemicals in the occupational environment. Governmental regulations have increased the number and types of medical laboratory screening required for a large variety of halogenated hydrocarbons as well as other potential environmental hazards. The primary objective of these screening programs is to reduce disability, morbidity and mortality in workers, especially as related to serious low-grade health hazards. In general, screening programs are instituted because of the presence in the work environment of a suspected or proven environmental toxin or carcinogen, which has the potential of producing low-grade injury over long periods of exposure.

Most screening studies are directed toward the detection of abnormalities in certain body systems. The specific tests are frequently selected on the basis of medical experience which utilized them in symptomatic or hospitalized populations. Prior experiences utilizing nonspecific multiphasic health surveillance screening and maintenance have not proven to be cost effective except under certain limited

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conditions (*1*). The cost effectiveness of such tests, however, in the determination of medical screening requirements, has played a limited role due to the potential seriousness of these occupational agents. Little attention has been paid as to whether the effectiveness of federally required screening provides the best or, more importantly, a necessary benefit when applied to asymptomatic and otherwise healthy worker populations.

The discovery in 1974 of hepatic toxicity and cancer formation in vinyl chloride workers provided the opportunity to systematically and prospectively study the effectiveness of federally required and federally recommended medical screening procedures for the detection of chemical liver injury, including cancer development (*2*). Table 1 lists the federally required medical screening procedures since 1974 for environments utilizing vinyl chloride or polyvinyl chloride. Table 2 lists the federally recommended studies for these same environments. This paper will present a preliminary assessment of the effectiveness of these federally required studies in the accurate detection and identification of chemically induced liver injury due to halogenated hydrocarbons, especially vinyl chloride.

Materials and Methods

The industrial population studied consisted of approximately 1200-1400 employees of a chemical plant whose two major products were synthetic rubber and plastics. The industrial plant had been in operation for over 35 years and had a predominance of male employees (96%), approximately 80-87% of the work force being white, 11-12% black, less than 1% of other racial origins. Turnover of the plant was approximately 10 to 15% per year with 65-70% of the work force having worked five years or more at the plant. Employee ages ranged from 18-65, with a mean of 52 years.

A cohort consisting of 969 male employees who worked continually from June 1, 1976 to May 31, 1977 was, for purposes of this analysis, divided into a "standard" and a "nonstandard" population. These designations were given on the basis of a review of all present standard medical data on each employee, including the federally required studies. Other screening studies of the medical surveillance programs were not utilized in the classification of overall medical status because, at that time, their clinical usefulness was unknown or controversial. All studies were performed on an annual basis. Those individuals with ten years or more of employment were examined and screened semiannually. Compliance with medical screening studies during the five-year study period showed a continuous participation in the history and physical examinations by over 75% of the work force, laboratory tests and chest x-rays by 86%, and liver-spleen scans by 85%. Seventeen percent failed to undergo at least one history and physical examination, 9% did not have any of the radiological studies, and only 4% failed to have laboratory studies during this period. Approximately 40-50% of these individuals who did not undergo an examination claimed to have been examined by their private physician.

A subcohort of 120 individuals was further identified based on the availability of a liver biopsy performed for medical reasons, both related and not related to their work.

The term "standard" is used for those individuals who, based upon the best medical opinion, demonstrated no evidence of any significant medical disease, occupational or nonoccupational in origin. The "nonstandard" population included all others not included in the standard population.

The subcohort population was divided into those individuals with and without histological evidence of liver injury and further subdivided into those with and without histological features characteristic of chemical injury.

All employees had individual work histories. These consisted of a standardized job classification for all jobs within the plant since its opening and a

Table 1. Federally required studies for vinyl chloride workers.

History and physical
< 10 years as vinyl chloride worker—(annual)
> 10 years as vinyl chloride worker—(semiannual)
Biochemical studies
SGOT (AST)
SGPT (ALT)
GGTP
AP
TB

Table 2. Federally recommended (not required) studies.

Hepatic studies
LDH isoenzyme
Total protein
Protein electrophoresis
Hb_SA_C
Radioisotopic scan
Kidney dysfunction (urine examination)
Albumin
RBC
Exfoliative abnormal cells
Pulmonary system
FVC
FEV_1
Chest x-ray (PA and lateral)

rank ordering of exposure for 22 different suspected or potentially hazardous heptatoxic chemicals used within the work place (*3-5*). The agents were rank ordered on the basis of the intensity of exposure for each of the job classifications for each of the years that the plant was in operation. From this detailed work history, a cumulative exposure ran month ration (CERM) was determined for each employee for each of the 22 chemicals. All histological material was classified as to the presence or absence of liver disease, and to whether the abnormalities were consistent with chemical or non-chemical injury. This classification was conducted double blindly by three experienced physicians, two pathologists, and a hepatologist (*6*), without knowledge of any medical data, exposure or work history.

Results

Although 50 or more biochemical screening tests were performed during this study period, this paper will limit itself to the evaluation of the federally required studies, the indocyanine green clearance (ICG) study at the 0.5 mg/kg dose (*7, 8*) and radioisotopic liver and spleen scan (*9*). The

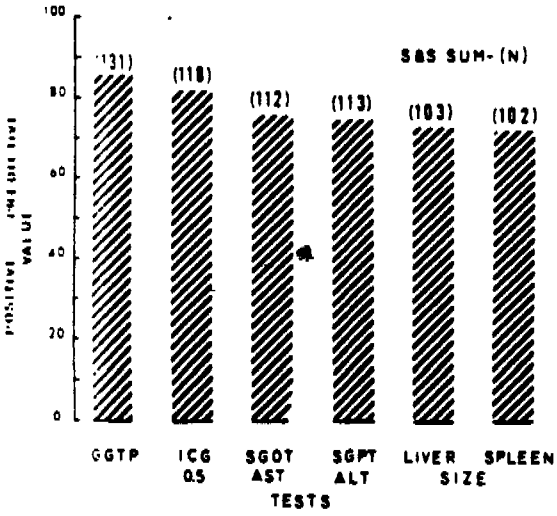

FIGURE 1. Positive predictive values of screening tests in identification of medical disease in an asymptomatic working population (N = 969). All those screening tests with positive predictive values of greater than 70 are shown except for indirect bilirubin (due to high number of congenital indirect hyperbilirubinemia) and triglyceride determination. Above each bar in the graph are shown the sum values for sensitivity and specificity of each test. They generally follow the same ranking.

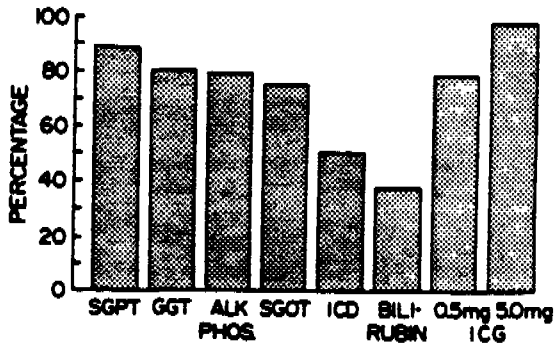

FIGURE 2. Frequency with which clinical biochemical tests correctly reflex the presence of hepatic damage in chemical workers suspected of having liver disease: (SGPT) alanine aminotransferase (ALT) (GGT) γ-glutamyl transpeptidase, (SGOT) aspartic aminotransferase (AST), (Alk. Phos.) alkaline phosphatase, (ICD) isocitric dehydrogenase (ICG) Indocyanine Green clearances at 0.5 and 5.0 mg/kg dose.

federally required biochemical studies include alkaline phosphatase (AP), γ-glutamyl transpeptidase (GGPT), alanine aminotransferase (ALT/SGPT), bilirubin (ALT/SGPT), and the aspartic aminotransferase (AST/SGOT).

The positive predictive values of these screening tests in identifying medical disease (including liver disease) in this asymptomatic working population are shown in Figure 1. The GGTP provided the highest positive predictive value as a screening test for "nonstandard" individuals. It also provided the highest sensitivity and specificity sum shown in brackets. The predictive value of the other tests, in decreasing positivity were ICG, AST, ALT, liver and spleen scan, AP, and bilirubin.

Further evaluations were conducted on the subcohort population in whom we had both histological and biochemical data concerning hepatocellular damage. If one looks at only those individuals who received liver biopsies for suspected liver disease then one would find the percent of positive tests as illustrated in Figure 2. The ALT (SGPT), GGTP, AP and AST (SGOT) demonstrate a very high degree of sensitivity in identifying individuals with hepatic disease. As shown on the right, ICG clearances at the 0.5 mg/kg level provide a similar degree of sensitivity to SGOT and AP. The higher dose ICG clearance (5 mg/kg) appears to provide the most sensitivity for latent hepatic disease. These findings are consistent with the general medical experience with hospitalized patients.

Sensitivity alone however is not an adequate indicator of a test's screening value, especially when used in asymptomatic individuals. More appropriate evaluation of these tests' value as screening instruments are shown by their sensitivity, specificity

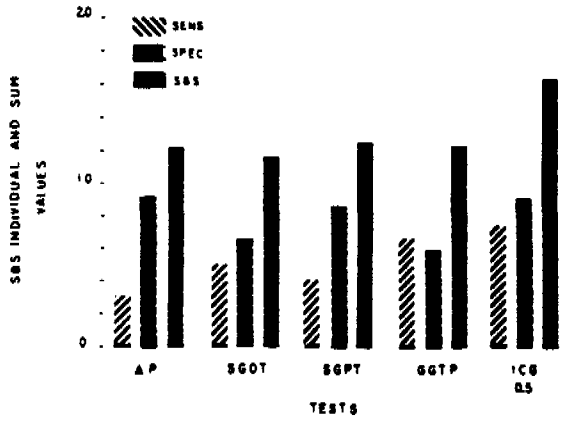

FIGURE 3. Sensitivity and specificity of various biochemical screening tests and their sensitivity and specificity sum values (S & S) based on 78 with biopsy documentation of their hepatic status and all of the biochemical screening studies listed. All screening tests with S & S sums less than 110 (e.g. bilirubin and isocitric dehydrogenase, are not illustrated.

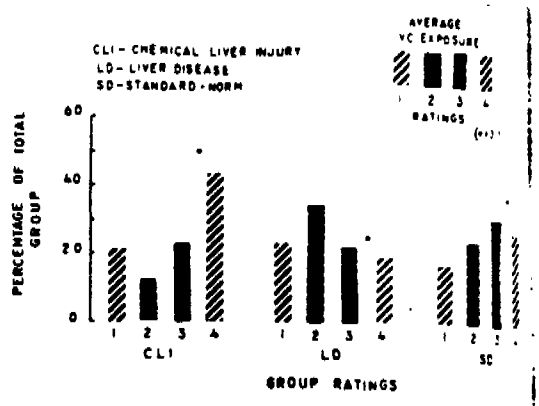

FIGURE 4. Correlation between the histologic findings on liver biopsy and each individual's average total vinyl chloride exposure based on their average CERM (Cumulative Exposure Rank Months) ratings. Rankings: 1 = lowest possible exposure; 2 = minimal exposure, low levels; 3 = moderate exposure; 4 = worked in areas subject to occasional high excursions, or frequently high and/or had intimate contact

and sum values shown in Figure 3 in the biopsied subpopulation. Here again, γ-glutamyl transpeptidase and ICG clearance (0.5 mg dose) show the greatest sensitivity for identifying individuals with liver disease. However, GGPT had the least specificity, reflecting its high incidence of false positives. Specificity increased with the use of AST, ALT, and ICG clearance. The alkaline phosphatase provided the highest specificity, suggesting that mild or low grade chronic hepatic injury due to environmental agents may be activating hepatic AP synthesis in the absence of biliary tract obstruction or cholestasis. The ICG clearances, even at the low dose (0.5 mg/kg), clearly remains the test with the best combined sensitive and specific screening study for detection of individuals with subclinical hepatic disease.

This subcohort biopsied group was further examined on the basis of the histological interpretation of their liver biopsies and their work exposure to vinyl chloride. All biopsied individuals were subdivided into three groups: 19 with histological evidence consistent with chemical liver injury; 30 with histological evidence of liver disease, nonchemical liver injury; and 29 with normal liver biopsies. Each of the histological subgroups were further subdivided based on their vinyl chloride exposure, on a scale of 1 to 4 (Fig. 4).

The chemical liver injury group contained the highest percentage of individuals with the highest average rating (CERM) for vinyl chloride exposure. In contrast, with those with liver disease, nonchemical, and those with normal livers have a more even distribution of individuals relative to their degrees of vinyl chloride exposure.

In our previous studies we noted that almost all individuals with histologically specific lesion of vinyl chloride injury or angiosarcoma had a total average CERM rating of 3.5 or greater. The asterisk in Figure 3 indicates the percentage of individuals in each of the three histological groups with exposure ratings of 3.5 or greater. Again, the chemical liver injury group have the highest percentage of individuals with the high exposure ratings. This further supports previous work (*4, 10*) identifying focal hepatocellular hyperplasia as the earliest histological characteristics of chemical injury in liver disease.

A study of the frequency with which these tests are positive among those individuals with liver disease, based on their histological findings (chemical versus nonchemical), provides additional data supporting the clinical observation that an increased AP has a greater specificity for chronic liver injury.

Figure 5 shows the ratio of the proportion of positive screening tests in those with histological chemical liver disease divided by the proportion of positive tests in those whose disease is not of chemical origin. All tests, independent of their sensitivity and specificity for liver injury, were more frequently abnormal in the presence of nonchemical, subclinical liver injury, except for AP. In contrast, AP was far more frequently abnormal in those individuals with chemical liver injury, which tended to be more chronic than acute and generally less severe.

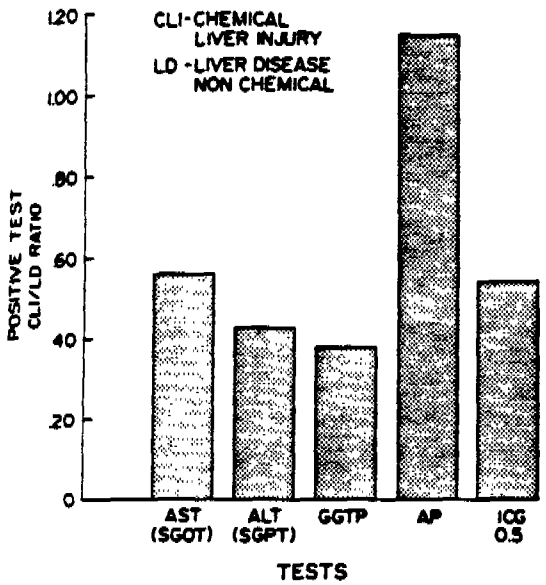

FIGURE 5. Frequency with which biochemical tests were abnormal in those with different type of hepatic injury expresses as a ratio: (CLI) chemical liver injury, (LD) liver disease, nonchemical.

Discussion

This preliminary systematic review of the positive predictive values and the sensitivity and specificity of federally and some non-federally required tests for chemical workers provides the first scientific and biological basis for the selection of medical screening tests for liver injury in occupational environments. Although these commonly used medical tests have been found by clinical experience to be effective as diagnostic tools in the symptomatically ill or hospitalized population, little clinical work has been done to determine their ability to accurately separate biological variations from early latent or underlying disease in asymptomatic individuals. Tests which provide very high false-positive rates (decreased specificity) such as GGTP, interfere with the screening process identification of the high risk worker by the extra time and cost required for repeat testing, the decreased productivity for the employer, the employees' increased anxiety, and by the loss of confidence in the effectiveness of the testing program by both employees and employer. Determination of the sensitivity and specificity of screening studies for asymptomatic individuals is essential if effective recommendations are to be made a federal requirement. This evaluation process also provided the best means of developing effective triage protocols for the screening program. For example, in this particular population of industrial workers, we have shown that the assessment of hepatic function is best accomplished by low dose ICG clearance (0.5 mg/kg). The ICG clearance is somewhat a more complicated technique (i.e., injection of substance and repeated blood sampling) but requires only 10 min to perform, and needs only one needle stick. In exchange it provides the best singular screening test for latent hepatic injury. If adequate medical facilities are not easily accessible, then ALT should be substituted. If either ICG clearance and/or ALT studies are found to be abnormal, an AP should be done and a diagnostic work-up instituted to determine the etiology (*11*).

The rationale for these recommendations is based on the actual study of chronic subacute chemical injury in an asymptomatic population, not preselected because of signs or symptoms. Therefore the test's ability to correctly differentiate disease from nondisease or one type of injury from another is more accurately determined. Chemical and environmental agents of low toxicity tend to produce repeated or persistent injury which accumulates over time. Tests which measure overall functional capacity quantitatively or semiquantitatively, rather than measuring acute low-grade injury over time are more likely to detect changes. For this reason, clearance or tolerance studies provide the best means for identifying latent hepatic disease, while enzyme studies like ALT, GGPT, and SGOT usually reflect acute cellular injury of higher grade or degree and cannot accurately reflex accumulative damage until very late in the disease process. Tests which provide information concerning the progression or nonprogression of injury will be far more helpful to the practicing occupational physician. They provide him/her with a better capability to discern between nonoccupational and occupational disease, and the best available reassurance for the worker of his or her safety while allowing the greatest possibility for continued productivity and employment.

Finally, these data provide a sound scientific basis upon which to modify federal requirements. The removal of specific testing requirements which, with field experience, prove not to have any significant positive predictive value, or effective sensitivity and specificity will aid in reducing overall cost and help maintain continued compliance by industry and workers. There may be theoretical reasons to maintain or continue some of the present federally required screening studies, but these reasons should be separately identified and not be confused with the purposes of the more effective test in the

detection of occupationally related liver injury.

The capabilities and limitations of any new tests or old tests for new screening purposes in detection of other potential occupational hazards, should be validated before making them a required screening procedure. This would lay the foundation for systematic determination of effectiveness of screening procedure against a proven standard. Unvalidated federal requirements provide the worker and employer with a false sense of security and safety by what is believed to be effective monitoring. More importantly, such a situation can lead to delay in effective correction of cause and disease prevention.

Conclusions

Biochemical screening for hepatic injury in asymptomatic chemical workers can be done most effectively by the use of liver specific clearance studies. ICG clearance provides the best combination of positive predictive value and sensitivity and specificity for functional hepatic testing at the present time.

None of the present federally required studies provide any significant degree of sensitivity without marked reduction in specificity in asymptomatic individuals.

The ALT (SGOT) is the most useful among those Federal tests presently required and the alkaline phosphatase may provide additional specificity as a follow-up study in those individuals with positive ICG or ALT screening studies.

There is no evidence that any of the other federal studies add any benefit and strong evidence that they significantly increase the false-positive results in well individuals.

All screening studies should undergo evaluation as to their positive predictive value and sensitivity and specificity in asymptomatic individuals before becoming permanent or established requirements.

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Poly(vinyl Chloride) Processes and Products

by R. N. Wheeler, Jr.*

Poly(vinyl chloride) resins are produced by four basic processes: suspension, emulsion, bulk and solution polymerization. PVC suspension resins are usually relatively dust-free and granular with varying degrees of particle porosity. PVC emulsion resins are small particle powders containing very little free monomer. Bulk PVC resins are similar to suspension PVC resins, though the particles tend to be more porous. Solution PVC resins are smaller in particle size than suspension PVC with high porosity particles containing essentially no free monomer. The variety of PVC resin products does not lend itself to broad generalizations concerning health hazards. In studying occupational hazards the particular PVC process and the product must be considered and identified in the study.

Poly(vinyl chloride) is a ubiquitous part of our environment today, in that it appears in clothing, upholstery, flooring, wire insulation, food containers, phonograph records and an almost infinite variety of other items. Despite this wide application and the size of the industry there is little public understanding of the term. A part of this confusion stems from the human inclination to abbreviate terms—thus, we say PVC when discussing poly(vinyl chloride) resins, poly(vinyl chloride) latexes, poly(vinyl chloride) compounds, poly(vinyl chloride) film and so forth. This confusion has been accentuated by governmental regulators, who define PVC as a polymer containing any amount of vinyl chloride. On taking these two factors into account it has become almost impossible to distinguish what is meant when the term PVC is used in the various media. In order to study possible PVC industry-related health problems one must know something of the various processes and products to properly evaluate study results. Many study results can have significance only if the source and composition of the PVC is stated.

Manufacture of synthetic resins from vinyl chloride and other monomers involves reacting these monomers in agitated pressure vessels in the presence of catalysts and converting these liquids and/or gases to solid resins. A considerable amount of heat is generated by the reaction. This is removed by cooling the vessel. As the monomer is converted to polymer during the reaction, the rate of reaction slows down; thus, after some optimum reaction time, the unconverted remaining monomer is removed from the reacting mass by heat and vacuum and the resin (PVC) is recovered as a dried white powder or as a liquid latex or solution. This polymerization reaction may take place in pure monomer, in a solution, in a water-monomer emulsion or in a water suspension of monomer. The nature of the polymerization process determines the nature of the subsequent recovery process, and the nature of the resin particles produced. Currently there are four basic vinyl chloride polymerization techniques which give use to the following four processes: (1) suspension polymerization, (2) emulsion polymerization, (3) bulk polymerization, and (4) solution polymerization.

Suspension polymerization is the major process used for the manufacture of PVC resins and is used for about 82–85% of U.S. production (Fig. 1). It involves the charging of one or two parts water and one part vinyl chloride monomer or comonomer mixture to an agitated reactor along with initiator and suspending agents such as poly(vinyl alcohol). The mass is reacted at 50–65°C until about 85–90% of the contained monomer is converted to resin. The resin-water mixture is heated, sometimes under vacuum, until the unconverted monomer is substantially removed. The resin is then removed

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from the water and dried in rotary, flash or fluid bed dryers by exposure to heated air. The dried resin is transferred to storage silos, whence it is shipped to fabricating plants in bulk containers or in paper bags. If only vinyl chloride monomer is reacted, the product is PVC homopolymer. If a monomer such as vinyl acetate is mixed with the vinyl chloride then a PVC copolymer is produced.

The advantages of the suspension resin process are its high productivity per unit reactor volume, its flexibility with regard to polymer composition and resin particle characteristics and the granular nature of its product. The relatively large resin particles (50 to 150 μm) cause problems in removing unconverted vinyl chloride monomer. The monomer tends to diffuse slowly from the center of the resin particle to the surface, where it is removed by the monomer recovery operation; thus removal often is incomplete. In the past, residual vinyl chloride monomer concentrations in suspension PVC resins ranged as high as 2000 ppm by weight until improved methods were developed in response to recognized need for lower residual levels.

The process produces a wide variety of products, each of which presents different monomer release characteristics as well as differing suitability for particular fabricating operations. As a general rule, small particle size resins have lower residual monomer than large particle size; porous particle resins have lower residual monomer than nonporous particle resins; and resins containing little or no comonomer have lower residual monomer than resins with significant amounts of comonomer. The relatively large suspension resin particle, while retaining monomer from the manufacturing process, results in a product that has excellent handling properties such as bulk flow. Recent improvements in monomer stripping technology have resulted in most PVC suspension homopolymer resins containing about 10 ppm residual vinyl chloride monomer at the time of shipment while the residual vinyl chloride monomer in most copolymers ranges from 25 to 200 ppm at the time of shipment.

The stress on residual monomer content at the time of shipment in the preceding paragraph is purposeful. Vinyl chloride monomer is not soluble in the PVC nor is it absorbed or adsorbed in the resin particle. It is entrapped, and, given an opportunity, it escapes to the ambient air. Heating tends to accelerate this escape. PVC resin in a bulk-container loses its residual monomer at a rate of 25 to 50% per month. PVC resin in a paper bag loses its residual vinyl chloride monomer at an approximate rate of 75% per week. Once the residual monomer is gone, there is no source of monomer from the PVC resin, i.e., the resin does not decompose to yield significant amounts of monomer. If heated, the resin gives off hydrogen chloride and turns black. Thus a year-old PVC resin contains almost no residual monomer: on heating until it blackens it will always give off hydrogen chloride. PVC resin fabricating operations drive off the free residual monomer in the first heating step; thus the probability of a toxic response from vinyl chloride monomer contained in the vinyl film or

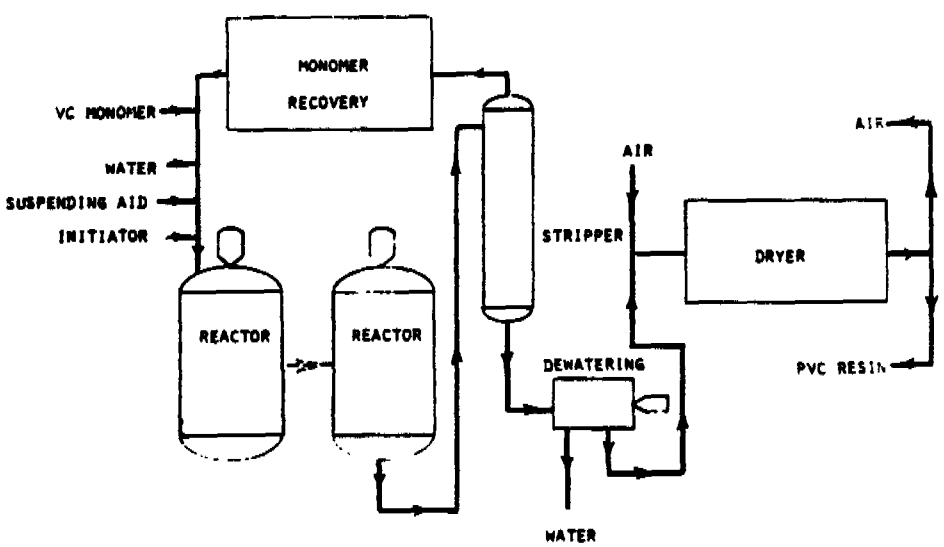

FIGURE 1. Suspension polymerization process.

moldings produced is remote.

All PVC processes have a problem with reactor system fouling to some degree. The conversion of a liquid monomer to a high molecular weight solid polymer while contacting reactor walls, baffles and so forth results in the deposition of some of that solid polymer on surfaces. This deposition or fouling interferes with the reactor operation so that periodically it has to be removed. In earlier times, this was removed manually by a man working in a shutdown reactor. These reactor cleaners were exposed to very high concentrations of vinyl chloride monomer (several thousand ppm). It was within the group of men in this cleaning operation that the excess of angiosarcoma was observed by Creech (1). More recently, techniques to minimize fouling and techniques for cleaning such as solvent washing and hydroblasting have reduced or eliminated the need for reactor entry and cleaning.

Emulsion polymerization is the second most widely used process for the manufacture of PVC resins and comprises 10–12% of total U.S. production. One of the important things to understand about emulsion polymerization is that it is not a single process but a large family of processes, each producing specialized products that are defined or specified in terms of performance in a particular application. In the interest of brevity, the two major process families will be discussed: the water-soluble initiator system and the oil-soluble initiator system (Fig. 2).

In the water-soluble initiator system, one to two parts water, one part monomer, 0.01 to 0.03 parts surfactant and water-soluble initiator (a redox system or a persulfate salt) are charged or fed to an agitated reactor and reacted at 30–60°C to form a synthetic latex. The reactor agitation must be sufficiently vigorous to emulsify the monomer-water mixture but not so vigorous that the latex is coagulated. When 80–95% of the monomer is converted to polymer, the latex may be gently stripped of the unconverted monomer with heat and vacuum, or it may be subjected to a second initiator treatment and reacted to essentially 100% monomer conversion. The product of this polymerization may be simply filtered and shipped to consumers as a latex for coatings, mastics, and the like, or the polymer may be recovered as a dry resin. Recovery techniques vary. The most commonly used is simply spray-drying of the latex, though some resins are recovered by coagulating the latex and dewatering with subsequent drying of the coagulum (resin).

In the oil-soluble initiator system, one part monomer containing an organic peroxide is emulsified in one to two parts water containing 0.01 to 0.03 parts surfactant. The resulting emulsion is reacted at 30–60°C to form a synthetic latex. Approximately 80–90% of the monomer is converted to polymer. After reaction, the latex is gently heated and vacuum-treated to remove the unconverted monomer. After stripping, the latex may be shipped as a product though most of it is converted to a dry powder by spray-drying. The basic difference between the oil-soluble initiator process and the water-soluble initiator is that the size of the emulsified monomer particle determines the resin particle size in the oil-soluble initiator process, while polymerization technique determines the resin particle size

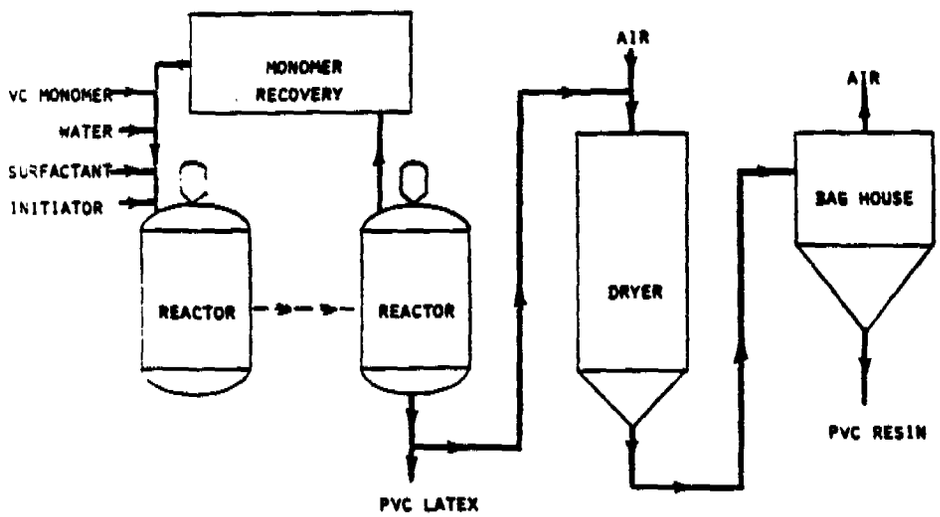

FIGURE 2. Emulsion polymerization process.

in the water initiator process. The resin particles formed during emulsion polymerization range in size from 0.05 to 2 μm. In the course of recovery and drying these may be agglomerated to particles as large as 30 μm. For some uses the agglomerates may be ground to a median particle size of about 2 μm. The small particle size results in rapid loss of residual vinyl chloride so that the resin contains about 1 ppm free monomer as produced. Because of handling problems, nearly all the resin is bagged, letting the small amount of monomer retained escape easily before it arrives at a fabricating plant.

Nearly all dried emulsion process PVC resin is utilized by paste or dispersion fabrication techniques. The resin, pigments and other additives are stirred into plasticizer, yielding a thick viscous liquid plastisol. This plastisol is spread on a cloth or a paper or poured into molds. The coated mold or cloth is heated, causing the resin and plasticizer to fuse into a solid forming the finished plastic article. In this fashion, the small manufacturer or the producer of elaborate shapes or highly styled items can make a product with a minimum capital investment.

The emulsion polymerization process, in addition to the reactor fouling problem noted for suspension polymerization, has less flexibility with regard to changes in process conditions. Each change in reaction, stripping or drying has an identifiable effect on product properties and quality. Some of these properties are well known, and quality tests keep them under control. Others are not well known and are recognized when customers complain. Emulsion process resins cost more to produce, and plant operators tend to be very conservative in the approach to process changes. Because of this difficulty, emulsion process plants tend to emit more vinyl chloride monomer to the ambient air per pound of resin produced. In Europe particularly there have been reports of worker dermatitis from surfactants and possible pneumoconiosis from resin dust inhalation in the emulsion process plants (2-4).

Bulk polymerization is the third major process in terms of volume for the manufacture of PVC resins but supplies only about 5% of U.S. production (Fig. 3). The process involves the charging of vinyl chloride monomer and initiator to a first-stage polymerizer, where about 10% of the monomer is converted to polymer. This batch is then transferred to a second-stage polymerizer where additional monomer, and sometimes initiator, are added. The polymerization is continued until about 80–85% of the container monomer is converted to polymer. The unreacted vinyl chloride is removed by heat and vacuum and the finished resin product transferred to storage bins for later shipment to fabricating plants. The absence of water in the polymerization stage eliminates the need for the drying step and provides some economy in capital and operating costs.

The advantages of the bulk process are its simplicity, the uniformity of the resin particle size, the high porosity of the resin particles and the purity of the polymer (no soaps or suspending aids). The disadvantages are: less flexibility in product mix (homopolymers only) than the suspension pro-

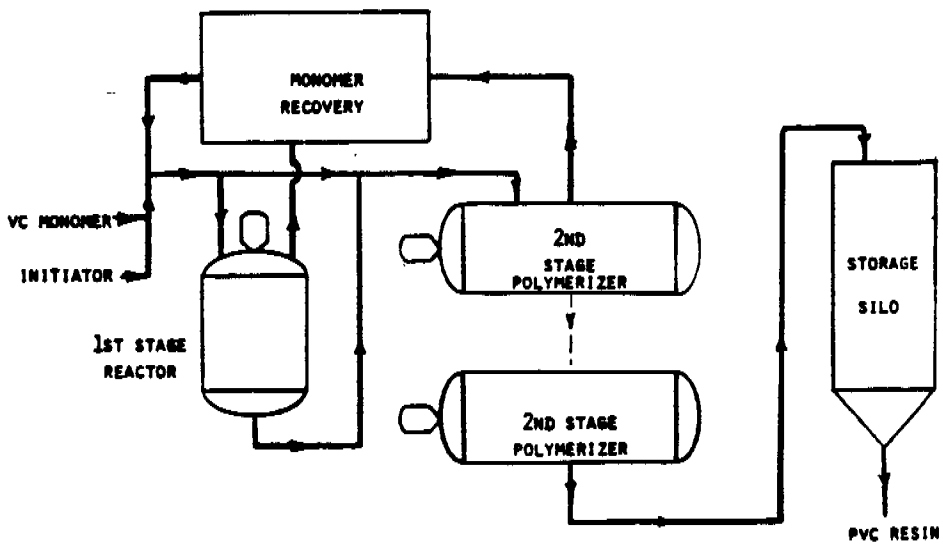

FIGURE 3. Bulk polymerization process.

ness and poorer removal of residual VCM. These bulk process resins are generally directly competitive with suspension process PVC homopolymers.

The relatively large porous resin particles (50 to 150 μm) tend not to retain monomer, thus removal of residual VCM is theoretically easy. The transfer of heat from the reactor wall to the resin particle for stripping is poor thus offsetting the advantages gained by the high particle porosity in removing residual VCM. In the early 1970s, residual VCM in this type of resin was of the order of 1000 ppm when produced, but more recently these resins have less than 50 ppm in residual VCM when produced.

Solution polymerization is a process unique to Union Carbide Corporation and accounts for about 2% of the total resin produced (Fig. 4). Vinyl chloride monomer, comonomer, solvent and initiator are fed to a continuous reactor system. The polymer formed is soluble in the reacting mass so that the reactor product is a viscous resin solution. This solution is distilled to remove the unconverted vinyl chloride monomer, and the resin product is recovered by treating the resin solution with water and drying the product. The resin particle is very porous, is always a copolymer, is free of soaps and suspending agents, has a median particle size of 75 μm and contains less than 0.2 ppm residual VCM. Manufacturing investment is high, and the product finds its greatest use as a coating material, i.e., paints and lacquers, that utilize its good dissolving qualities. It is used in relatively small quantities, and is nearly always shipped in bags rather than bulk.

In addition to the basic PVC resins described earlier, there is a wide variety of resin powders, pellets, liquids and latexes in commerce that fall under the general designation of PVC. These are chemically or mechanically converted PVC resins such as post-chlorinated resins and compounded resins containing plasticizers, stabilizers and the like. As a general rule, the additional processing has removed essentially all of the residual VCM and agglomerated the dusts. Converted PVC resins have no involvement with problems related to vinyl chloride monomer exposure.

Conclusions

Poly(vinyl chloride) resins are produced by four basic techniques: suspension, emulsion, bulk and solution polymerization.

The variety of PVC resin products does not lend itself to broad generalizations concerning hazards to worker health.

In evaluating occupational hazards, the PVC process, the PVC product and other materials present must be considered before valid conclusions can be reached.

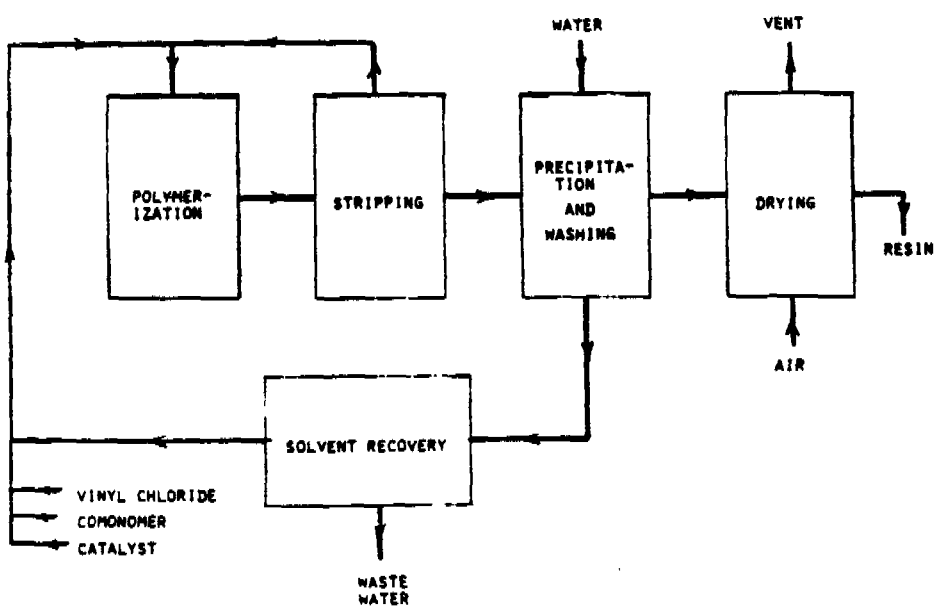

FIGURE 4. Solvent vinyl resin process.

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Worker Exposure to Vinyl Chloride and Poly(vinyl Chloride)

by James H. Jones*

The National Institute for Occupational Safety and Health (NIOSH) in early 1974 began industrial hygiene studies of vinyl chloride exposed workers. Three VC monomer plants, three VC polymerization plants, and seven PVC fabrication plants were surveyed. VC polymerization plant workers and workers in one job category in VC monomer plants were exposed to average levels above 1 ppm. The highest average exposure was 22 ppm. NIOSH health hazard evaluation studies since these initial surveys have primarily shown nondetectable levels of vinyl chloride. A NIOSH control technology study in 1977 showed that exposure levels in VC polymerization plants had been drastically reduced but exposure levels above 1 ppm were still found in several cases.

Introduction

The National Institute for Occupational Safety and Health (NIOSH) began studies of vinyl chloride (VC) early in 1974 following a report of increased incidence of angiosarcoma of the liver among VC exposed workers. A part of this work included retrospective cohort mortality and industrial hygiene studies of the VC polymerization industry. Also, NIOSH contracted with Bendix Corporation, Launch Support Division, to conduct industrial hygiene studies in the VC monomer production industry and the polyvinyl chloride (PVC) fabrication industry. These industrial hygiene studies were done to document the levels of VC exposure occurring in industry at that time. Three VC monomer plants, three VC polymerization plants and seven PVC fabrication plants were studied. In addition to the VC industry-wide study, NIOSH, through their health hazard evaluation (HHE) program has sampled for PVC at 34 other plants, primarily VC fabrication operations. Also a study to document control methods utilized in the plastics industry was performed under contract by Enviro Control. This study included work at five VC polymerization plants (*1-36*).

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Industry-Wide Study

VC Monomer Plants

One of the VC monomer plants sampled used the acetylene-hydrogen chloride process, the older process for making VC, and the other two used the ethylene dichloride pyrolysis process. It was not possible to assess the difference in worker exposure between the two processes because the plant using the acetylene-hydrogen chloride process was operating at only 10% capacity during the surveys in December 1974.

As can be seen in Figure 1, only the job of loader shows exposure substantially above 1 ppm. VC exposure for this job was being reduced, at the time of the surveys, by the redesign of tank car hookup systems and the use of air-supplied breathing apparatus while the tanks cars were connected or disconnected.

VC Polymerization Plants

Three VC polymerization plants were sampled. Located at these plants were three suspension resin operations, three dispersion resin operations, one mass resin operation and one solvent resin operation. As can be seen in Figure 2, suspension and dispersion resin operations had the highest exposure levels. Within plants the reactor area operators and helpers had the highest exposures.

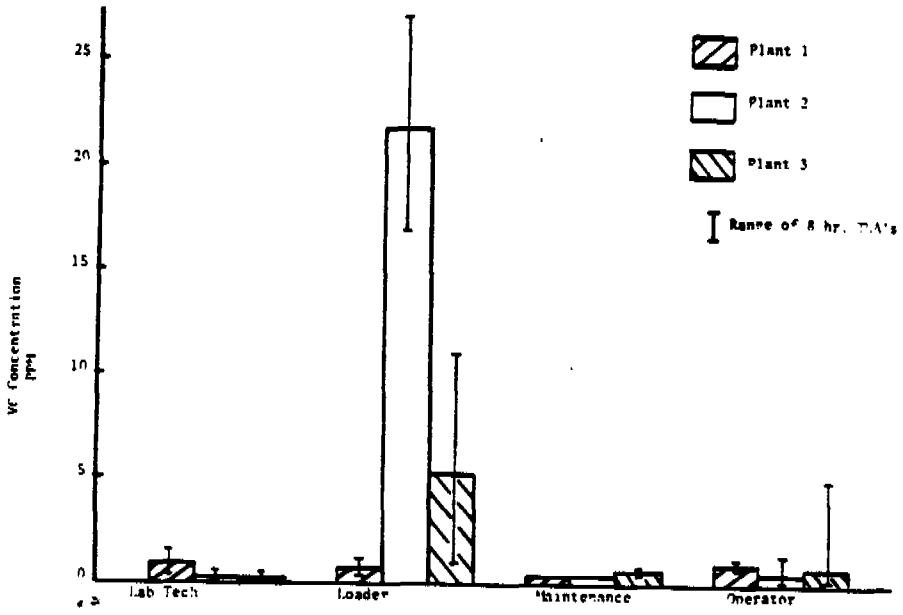

FIGURE 1. Means and ranges of VC exposures in VC monomer production plants.

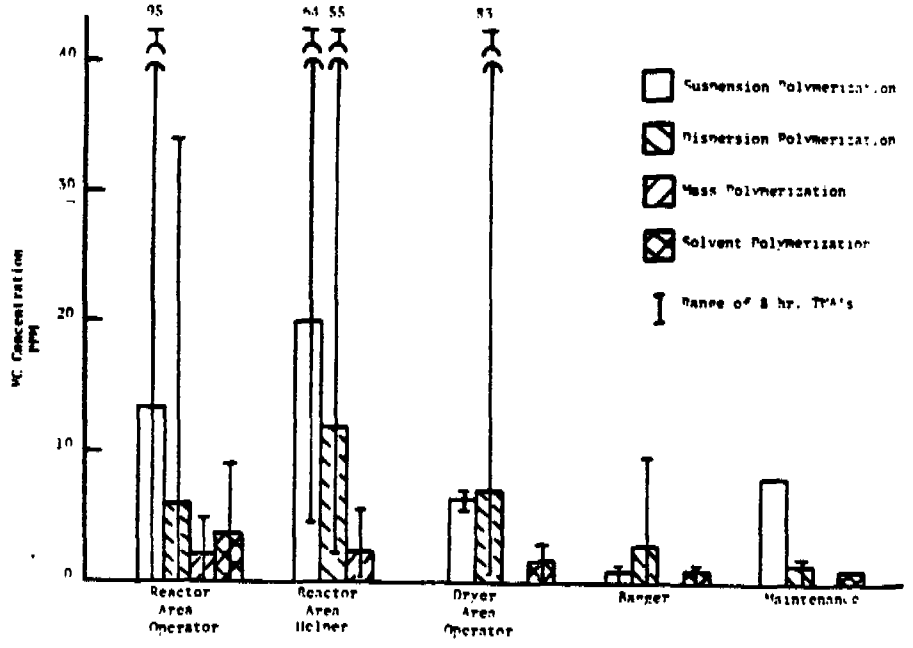

FIGURE 2. Means and ranges of VC exposures in VC polymerization plants.

PVC Fabrication Plants

In the seven PVC fabrication plants samples were collected in calendering, compounding, extrusion, molding, and plastisol operations. All exposures were quite low with calender operators having the only exposures above 1 ppm. Figure 3 shows the relationship of VC exposure between the segments of the PVC industry. As would be expected, VC polymerization had the highest exposures and PVC fabrication the lowest.

Changes in Exposure Since 1974

We have no information generated by NIOSH and know of none in the literature on how VC monomer plant exposures have changed since 1974, although it would be expected that the single "high" exposure category, loader, has had exposure reductions.

Information on how well VC polymerization plants were able to reduce exposures since 1974 was obtained during the control technology study. This information is in the form of company personnel sampling data for VC over a period of time. At the first plant, a mass polymerization plant, the percentage of personnel samples below 1 ppm has gone from 2% in 1974 to 73% in 1976 (Fig. 4). At the second plant, a suspension and dispersion polymerization plant, the percentage of personnel samples below 1 ppm has gone from 0% in 1974 to 65% in 1977 (Fig. 5). At the third plant, a mass polymerization plant, VC exposures are given by job for the period October 1974 to May 1975 and then for January 1977. In Figure 6, it can be seen that exposures dropped substantially, in most cases by a factor of almost 10. VC exposures at the fourth plant, a suspension polymerization plant, are given for both 1975 and 1976. As seen in Figure 7, in most cases a two-fold drop in exposure levels occurred. Although the percentage drop is lower than the third plant, the final exposures are about the same. At the fifth plant, a dispersion polymerization plant (Fig. 8), VC exposures are given by job for the period May 1975 to December 1975 and then for January 1976 to September 1976. Again reductions were sufficient to bring exposure averages to the same approximate level (less than 1 ppm) as the preceding two plants.

PVC fabrication plants had exposures predominantly below 1 ppm in early 1975 when the industry-wide study was done. In addition to this work, HHE's have been conducted at 26 PVC fabrication plants beginning May 1974 and ending in April 1978. Detectable levels of VC were found in only 10 plants with only 1 plant of the 15 sampled since April, 1975 having detectable levels. At that plant sampled in March, 1976, the highest level found was 0.38 ppm.

PVC dust exposures were also briefly examined

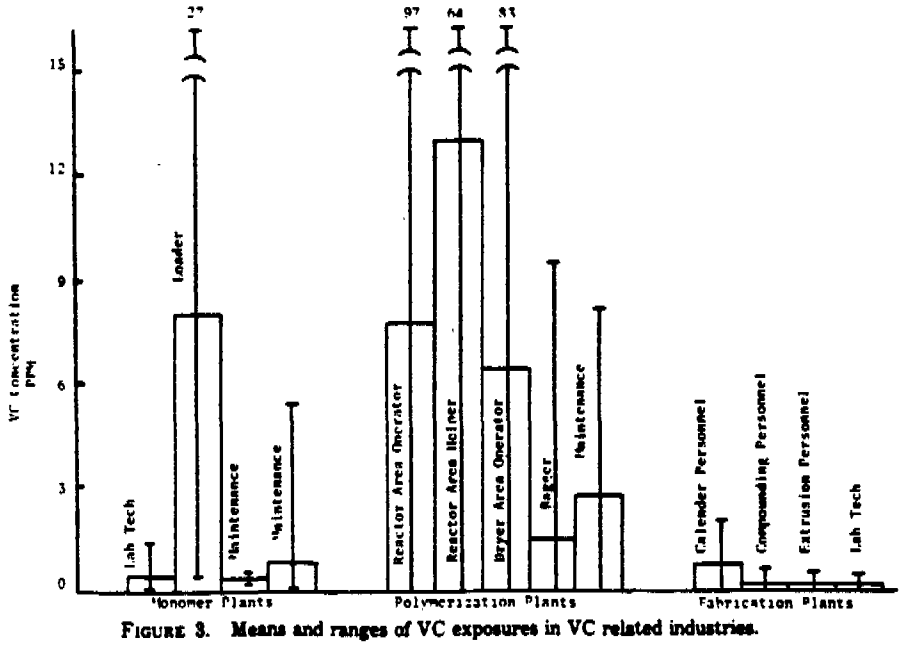

FIGURE 3. Means and ranges of VC exposures in VC related industries.

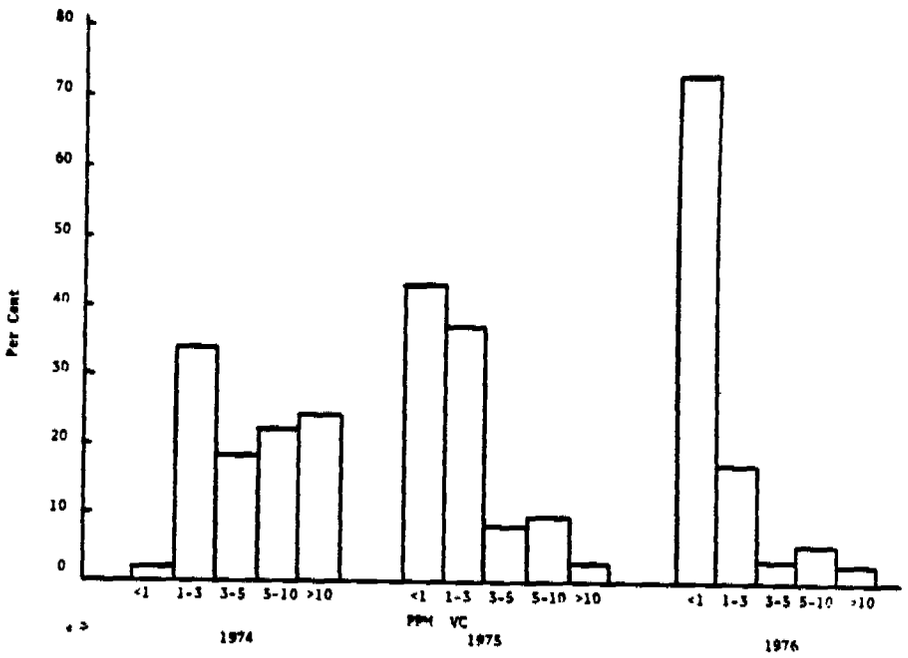

FIGURE 4. Distribution of VC exposures at a mass polymerization plant.

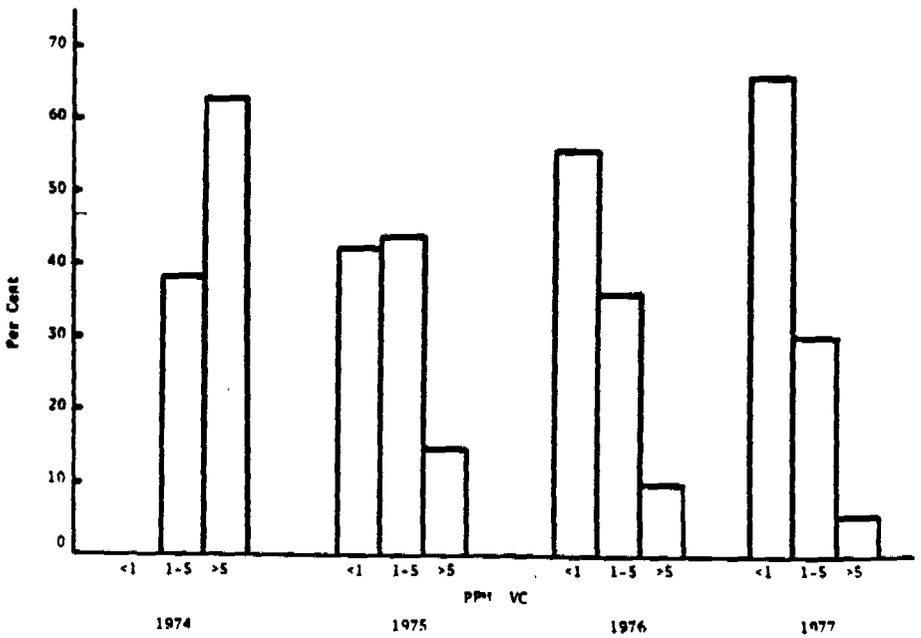

FIGURE 5. Distribution of VC exposures at a suspension and dispersion polymerization plant.

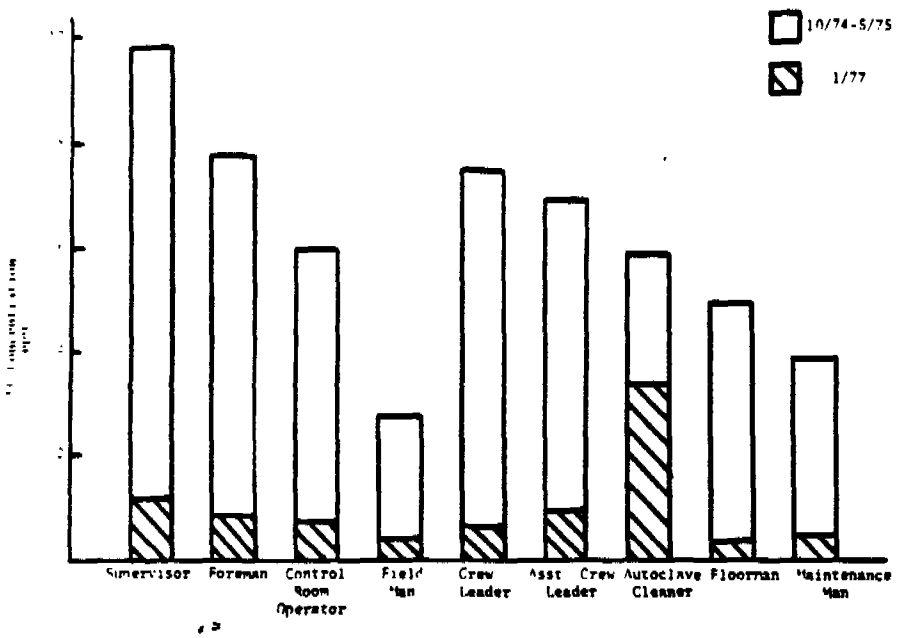

FIGURE 6. Change in VC exposures at a mass polymerization plant.

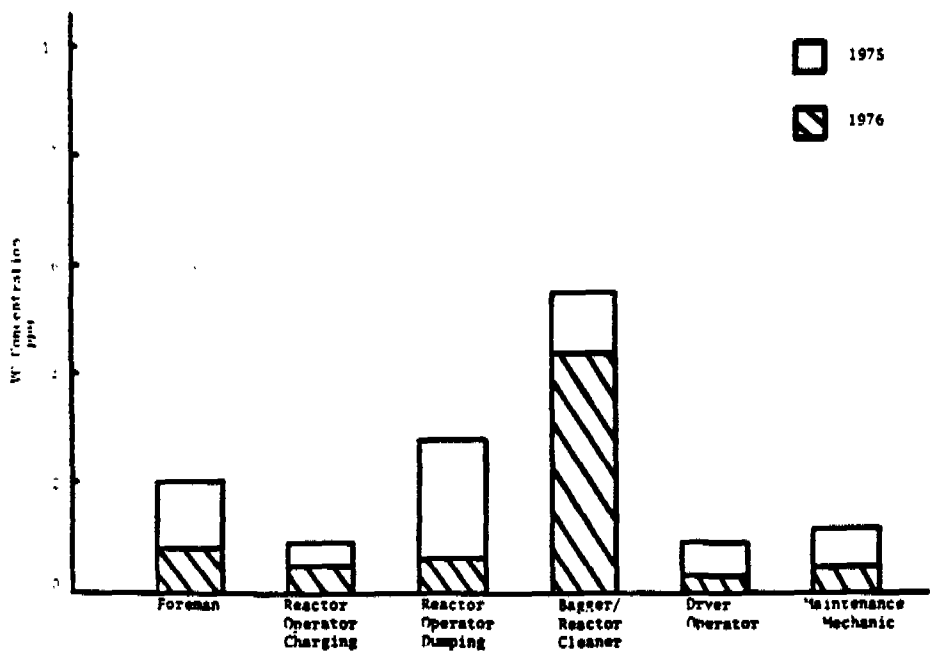

FIGURE 7. Change in VC exposures at a suspension polymerization plant.

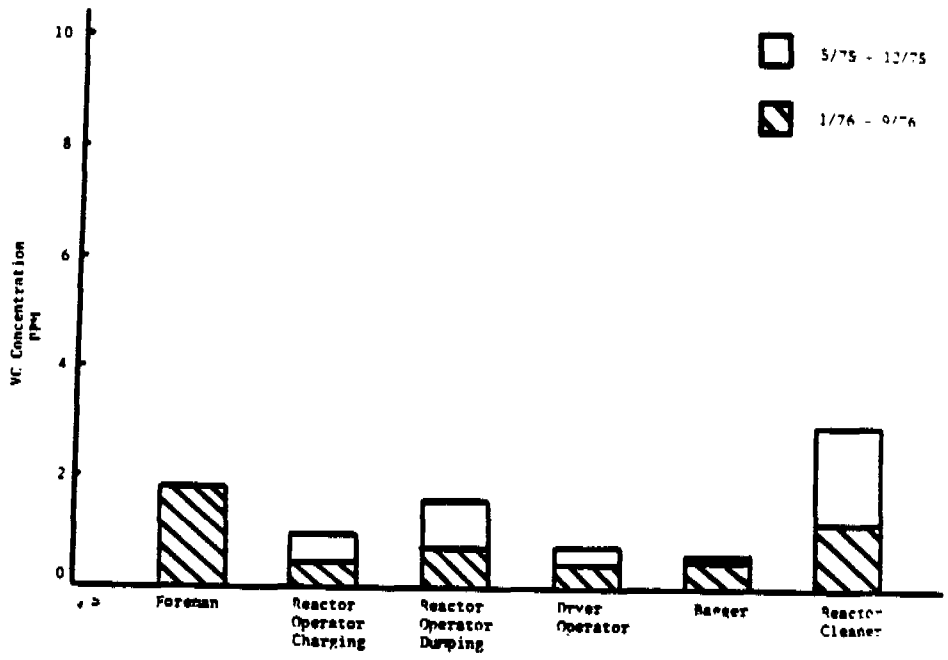

FIGURE 8. Change in VC exposures at a dispersion polymerization plant.

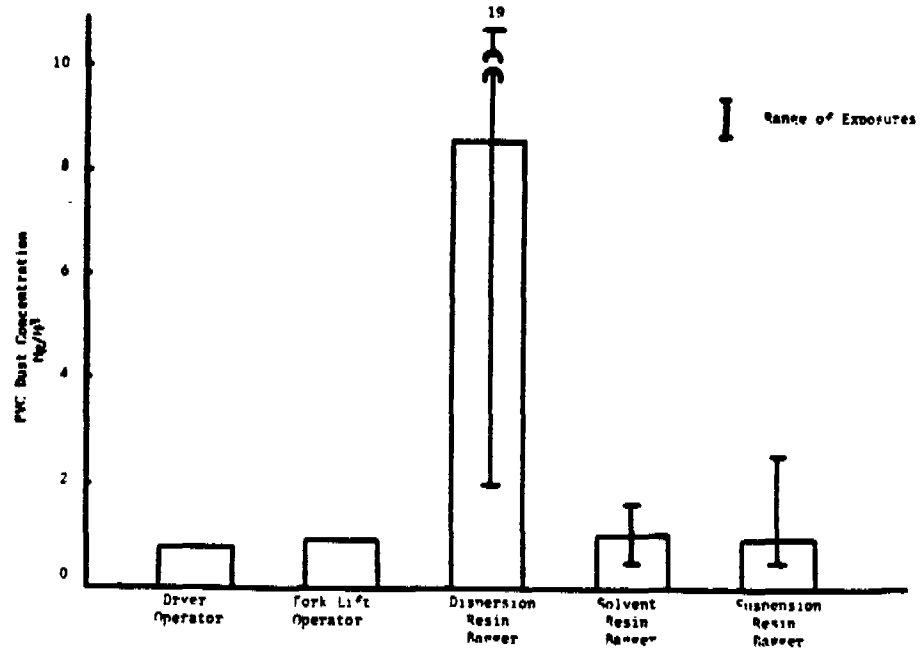

FIGURE 9. PVC dust exposures at VC polymerization plants.

during the industry-wide study. Total dust concentrations were determined. Because it was felt that PVC would be the primary constituent of the dust, no analysis for PVC was performed. Respirable samples were not collected because it was felt that the static charge on PVC particles would cause malfunctioning of the normally used sampling equipment, such as nylon cyclones. A few samples were examined by optical microscopy. In these samples all particles had diameters less than 7 μm, and 90% of the particles had diameters less than 2.5 μm. The samples examined were from dispersion resin operations.

This result was expected, since dispersion resins generally are in the range of 2-10 μm in diameter. Suspension resins, the major resins in terms of production, are generally much larger, about 100 μm in diameter. The sampling results displayed in Figure 9 show that dispersion resin bagging had by far the highest exposure, averaging 8.6 mg/m^3. We have no information on whether PVC dust exposures have been reduced since 1974.

It appears, based on the information that we currently have that the PVC fabrication industry has achieved good control of VC exposures. The VC polymerization industry was making big strides in controlling exposures, but we have no information to tell if they have continued to lower exposures since 1977. We have no information on exposure reductions in the VC monomer production industry, but it appeared that only one job category was significantly above the standard in 1974.

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Mortality Among PVC-Fabricating Employees

by Leonard Chiazze, Jr.,* and Lorraine D. Ference*

The results of a cross-sectional mortality study of 3847 deaths occurring among current and former (white) employees of 17 PVC fabricators during 1964-1973 are presented. Sex-race-cause-specific proportionate mortality ratios (PMR's) were computed by using two separate standards: one, the U.S. mortality in 1968; the second, U.S. mortality for the individual years 1964-1973. In addition, a case-control analysis, based upon 44 breast cancer deaths among white female employees, is presented. PMR's are significantly different from unity for all cancers, and for cancers of the digestive system among both white males and white females. Although observed deaths significantly exceeded expectations for cancer of the breast, a subsequent case-control analysis reveals no statistically significant relative risks for breast cancer.

Introduction

In March, 1974, Organization Resources Counselors (ORC) was requested by representatives of PVC producers who are members of ORC's Occupational Safety and Health Standards Group, to carry out a study of health risks to employees working in the PVC fabricating industry. After considering a number of alternative study designs, it was decided that a cross-sectional mortality study would best meet the need for providing information as rapidly as possible. Details regarding reasons for selecting this type of study, the actual study design and results of the inquiry have been reported previously (*1*).

In the original report, proportionate mortality ratios were calculated according to the method of Guralnick (*2*) and by using the sex-cause-age specific distribution of deaths among U.S. whites in 1968 as the basis for determining expectation (*3*). For the current report, we have analyzed the data using the Mantel-Haenszel procedure both for determination of PMR's and in order to test whether PMR's differ significantly from unity (*4*, *5*). In addition, PMR's are presented using two separate standards as the basis for expectation.

A follow-up to the cross-sectional mortality investigation, utilizing deaths among white women for whom the underlying cause of death was cancer of the breast, was undertaken (*6*), and results of the case-control analysis will be presented.

Materials and Methods

Although alternative study designs were considered, several factors led to the decision to carry out a cross-sectional mortality study. First, the primary study objective was to determine relatively quickly whether any angiosarcoma deaths could be identified among the study group and this was best accomplished by examining causes of death among relatively recent decedents. Second, it would not have been possible to identify clearly and completely (if at all) the cohort of workers necessary for a historical cohort mortality study within a reasonably short period of time. As a result, the study was based upon 4336 deaths which occurred during the years 1964-1973 among active or retired employees of 17 companies engaged in PVC fabrication (Table 1). This report will be restricted to the 3847 deaths among whites, since the number of deaths for most causes among nonwhites was quite small, making interpretation of cause specific mortality difficult at best.

Since the population at risk could not be deter-

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Table 1. Distribution of deaths among employees of 17 PVC fabricators by race and sex, 1964–1973.

Race	Total	Sex		
		Male	Female	Unknown
Total	4336	3676	658	2
White	3847	3252	595	0
Nonwhite	198	174	24	0
Unknown	291	251	39	2

mined, mortality rates as measures of risk could not be calculated. Rather, results are summarized in terms of proportionate mortality ratios (PMR) calculated according to the method of Mantel-Haenszel (5). Two separate standards have been employed. The first is the sex-cause-age specific distribution of deaths among U.S. whites in 1968 (1968 Standard). A second standard employs the sex-cause-age specific distribution of deaths among U.S. whites in each of the years 1964-1973 (1964-1973 standard). Cause-specific PMR's based upon the 1968 standard are adjusted for age, race and sex. Cause-specific PMR's based upon the 1964-1973 standard are adjusted for year of death as well as for age, race and sex.

The Mantel-Haenszel procedure for assessing the statistical significance of a difference between the observed and expected numbers of deaths for a specific cause requires the construction of a series of 2×2 contingency tables as shown in Table 2. Separate tables are constructed for each level of the factor(s) to be adjusted for. If, for example, we wish to compute a PMR for all decedents for cause X, adjusted for age (five age groups) and year of death (10 years: 1964-1973), i.e., 1964-1973 standard, we would have 50 2×2 tables: age < 35, year of death 1964; age < 35, year of death 1965; . . . ; age < 65, year of death 1973. Observed deaths and expected deaths are summed over the 50 separate 2×2 tables to produce a PMR for cause X, adjusted for age and year of death. The resulting age-year of death-adjusted PMR compares the number of deaths from cause X observed in the study group to the number of deaths from cause X expected in the study group, if the proportion of total deaths ascribed to cause X was the same, age group by age group and year by year, as for the comparison group.

Table 2. Construction of 2×2 contingency tables.

	Number of deaths in group I, attributed to		Total deaths
	Specified cause	Other causes	
Study group	A_i	C_i	N_{1i}
Standard	B_i	D_i	N_{2i}
Total	M_{1i}	M_{2i}	T_i

The statistical significance of the PMR (a test of the hypothesis that the PMR is 1.0 against the alternative that the PMR is different from 1.0) is evaluated by using the Mantel-Haenszel continuity corrected chi-square with one degree of freedom, i.e.,

$$\chi_{MH}^2 = \frac{(|\Sigma A_i - \Sigma E(A_i)| - \frac{1}{2})^2}{\Sigma \text{ Var } A_i} \quad (1)$$

where

$$\text{Var } A_i = \frac{N_{1i}N_{2i}M_{1i}M_{2i}}{T_i^2(T_i - 1)}$$

$E(A_i)$ = Expected value of $A_i = (M_{1i}N_{1i})/T_i$

The case-control analysis is based on 44 deaths among white females in the study with cancer of the breast as the underlying cause of death. Controls were drawn from deaths due to diseases of the circulatory system and accidents, and matched by age plus or minus five years and company, if possible. Forty of the cases were matched on both criteria and four on the basis of age alone. The basis for the case-control analysis, then, is the 44 breast cancer deaths and 134 matched controls distributed among eight of the 17 companies.

Results

Proportionate Mortality Ratios

Cause specific PMR's adjusted for age are presented for white male and white female employees in Tables 3 and 4. For Table 3, expected numbers of deaths are based on the cause-sex-age specific distribution of deaths among U.S. whites applied to the study group. For Table 4, PMR's are adjusted for year of death as well as race, sex and age. Statistically significant departures from unity (i.e., PMR = 1) are evaluated by using the Mantel-Haenszel continuity corrected chi-square with one degree of freedom. Causes of death for which the calculated chi-square indicated a statistically significant excess or deficit at the $\alpha = 0.05$ level of significance are indicated in the table. It is important to remember that when carrying out a large number of significance tests, some number will turn out to be significant on the basis of chance alone. When dealing with a large number of tests for PMR's, it may be more appropriate to consider the Mantel-Haenszel test as a screening device rather

...giving it a strict probabilistic interpretation. With these caveats, we see that based upon the ... standard, among white males there are statistically significant PMR's for all cancers, digestive cancer, respiratory cancer and other and unspecified cancers (Table 3). Among white females, PMR's are significantly different from one for all cancers, digestive cancers, breast cancer, urinary cancer and other and unspecified cancers. In contrast to white males, the PMR for urinary cancer among white

Table 3. Observed deaths and cause specific proportionate mortality ratios (PMR) for employees of 17 PVC fabricators by sex (white only), 1964–1973 (expectations based on U.S. mortality, 1968).

...se of death	ICDA 8th Revision	Male		Female	
		Observed deaths	PMR	Observed deaths	PMR
... causes	000–999	3252	1.0000	595	1.0000
...t cancer	140–209	670	1.1906[a]	181	1.3266[a]
Buccal cavity and pharynx	140–149	15	0.8382	3	—
Digestive organs and peritoneum	150–159	212	1.3056[a]	53	1.5134[a]
Stomach	151	41	1.3000	8	1.6226
Large intestine	153	72	1.3688[a]	24	1.5785[a]
Rectum	154	26	1.3230	5	2.0622
Liver	155	6	1.4306	0	—
Pancreas	157	37	1.1307	7	1.1612
Other and unspecified digestive	152, 156, 158, 159	30	1.3961	6	1.3680
Respiratory system	160–163	206	1.1647[a]	12	1.0119
Larynx	161	9	1.0695	0	—
Trachea, bronchus and lung	162	194	1.1704[a]	12	1.0788
Other	160, 163	3	—	0	—
Breast	174	0	—	44	1.3710[a]
Female genital organs	180–184	—	—	19	0.8232
Cervix	180	—	—	5	0.6827
Corpus	181, 182	—	—	6	1.2911
Ovary	183	—	—	7	0.6714
Other	184	—	—	1	—
Male genital organs	185–187	42	0.7986	—	—
Prostate	185	41	0.8223	—	—
Other	186, 187	1	—	—	—
Urinary organs	188–189	37	1.1153	11	2.9296[a]
Bladder	188	20	1.0053	4	—
Kidney	189	17	1.2800	7	3.4535[a]
Brain and nervous system	191–192	16	1.1499	4	—
Lymphomas	200–203, 205, 209	44	1.3560	9	1.1900
Leukemias	204–207	19	0.8117	1	—
Other and unspecified cancers	170–173, 190, 193–199	79	1.6132[a]	25	1.9584[a]
Other causes					
Diabetes	250	43	0.8655	10	0.6540
Diseases of circulatory system	390–458	1980	1.0516[a]	278	0.9067[a]
Heart disease	(390–398), 402, 404, (410–429)	1496	1.0625[a]	188	0.9009
Rheumatic heart disease	393–398	16	0.6373	7	0.7502
Hypertensive disease	400–404	36	1.0575	3	—
Ischemic heart disease	410–413	1381	1.0599[a]	158	0.8644[a]
Myocardial infarction	410	896	1.1040[a]	93	0.9688
Cerebrovascular disease	430–438	290	0.9913	65	0.9133
Other circulatory	450–458	40	1.5294[a]	8	1.2396
Diseases of respiratory system	460–519	144	0.6344[a]	17	0.5804[a]
Cirrhosis of liver	571	42	0.6575[a]	3	—
Cholelithiasis, cholecystitis and cholangitis	574–575	7	1.1018	3	—
Accidents, poisonings and violence	800–999	157	0.7007[a]	46	1.1364
Accidents	800–949	134	0.7043[a]	37	1.3369
Suicide	950–959	39	0.7427	2	—
All other causes	Residual	229	1.0410	57	1.1500

[a]PMR significantly different from one at $\alpha = 0.05$.

females is high and, although based upon only 11 deaths, is statistically significant. On the other hand, in contrast to the observation in white men, the PMR for respiratory cancer among white women is very close to unity. Similar to the observation in white men, mortality from cirrhosis of the liver is low, but the corresponding number of observed deaths is quite small.

Among both white male and female employees diseases of the circulatory system account for a large percentage of total deaths. In each case observed numbers of deaths are close to expected

Table 4. Observed deaths and cause specific proportionate mortality ratios (PMR) for employees of 17 PVC fabricators by sex (white only), 1964–1973 (expectations based on U.S. mortality, 1964–1973).

Cause of death	ICDA 8th Revision	Male		Female	
		Observed deaths	PMR	Observed deaths	PMR
All causes	000–999	3252	1.0000	595	1.0000
All cancer	140–209	670	1.1567[a]	181	1.2959[a]
Buccal cavity and pharynx	140–149	15	0.8340	3	—
Digestive organs and peritoneum	150–159	212	1.2667[a]	53	1.4813[a]
Stomach	151	41	1.3084	8	1.6541
Large intestine	153	72	1.3239[a]	24	1.5490[a]
Rectum	154	26	1.3164	8	2.1165
Liver	155	6	0.9801	0	—
Pancreas	157	37	1.1202	7	1.1461
Other and unspecified digestive	152, 156, 158, 159	30	1.3139	6	1.4549
Respiratory system	160–163	206	1.1155	12	0.9100
Larynx	161	9	1.0563	0	—
Trachea, bronchus and lung	162	194	1.1266	12	0.9787
Other	160, 163	3	—	0	—
Breast	174	0	—	44	1.3448[a]
Female genital organs	180–184	—	—	19	0.8161
Cervix	180	—	—	5	0.6869
Corpus	181, 182	—	—	6	1.2735
Ovary	183	—	—	7	0.6597
Other	184	—	—	1	—
Male genital organs	185–187	42	0.7687	—	—
Prostate	185	41	0.7964	—	—
Other	186, 187	1	—	—	—
Urinary organs	188–189	37	1.0942	11	2.8365[a]
Bladder	188	20	0.9884	4	—
Kidney	189	17	1.2517	7	3.4206[a]
Brain and nervous system	191–192	16	1.1267	4	—
Lymphomas	200–203, 206, 209	44	1.3525	9	1.1944
Leukemias	204–207	19	0.8019	1	—
Other and unspecified cancers	170–173, 190, 193–199	79	1.5975[a]	25	1.9564[a]
Other causes					
Diabetes	250	43	0.8993	10	0.6743
Diseases of circulatory system	390–458	1930	1.0538[a]	278	0.9132[a]
Heart disease	(390–398), 402, 404, (410–429)	1495	1.0600[a]	188	0.9035
Rheumatic heart disease	393–398	16	0.7090	7	0.8009
Hypertensive disease	400–404	36	1.1541	3	—
Ischemic heart disease	410–413	1381	1.0512[a]	158	0.8522[a]
Myocardial infarction	410	898	1.1148[a]	93	0.9962
Cerebrovascular disease	430–438	290	1.0011	65	0.9184
Other circulatory	450–458	40	1.5062[a]	8	1.2256
Diseases of respiratory system	460–519	144	0.6883[a]	17	0.6546
Cirrhosis of liver	571	42	0.6439[a]	3	—
Cholelithiasis, cholecystitis and cholangitis	574–575	7	1.1586	3	—
Accidents, poisonings and violence	800–999	187	0.6991[a]	46	1.1173
Accidents	800–949	134	0.7084[a]	37	1.3266
Suicide	950–959	39	0.7034[a]	2	—
All other causes	Residual	229	1.0246	57	1.1197

[a]PMR significantly different from one at $\alpha = 0.05$.

Table 5. Distribution of 44 breast cancer deaths and 134 matched controls by exposure category.

Exposure category	Breast cancer, cases		Matched control	
	Number	%	Number	%
No exposure	27	61.4	97	72.4
Improbable exposure	6	13.6	17	12.6
Possible exposure	0	0	4	3.0
Definite exposure	2	4.5	6	4.5
Unknown exposure	9	20.5	10	7.5
	44	100	134	100

although statistically significant.

Results based upon the 1964-1973 standard are, in general, consistent with those on the 1968 standard (Table 4). There are, however, some notable exceptions. In general, the PMR's based upon the 1964-1973 standard are lower than those based upon the 1968 standard. Further, the PMR for respiratory cancer among white males is not significantly different from one when based on the 1964-1973 standard. Among white women, the PMR for other (noncancer) respiratory deaths is significantly below unity based on the 1964-1973 standard.

Case-Control Analysis

Comparison of cases and controls on a variety of variables where information was available, including length of employment, ever married versus never married, and child-bearing history, reveals no statistically significant differences ($p > 0.05$) between cases and controls for any of these variables.

Review of employment histories for cases and controls revealed a wide variety of jobs ranging from office and clerical work to production jobs such as bench inspector, press operator, trimmer, assembler and sweeper. The wide range of job content and location made it impossible to determine precisely whether there was PVC exposure in every case, or the precise length of that exposure. Therefore, a subjective ranking system was developed to classify exposures. Work histories were reviewed with plant personnel and PVC exposure potential was categorized into five classes—no exposure, improbable exposure, possible exposure, definite exposure and unknown exposure. This classification scheme enabled some definitive exposure statement in 80% of the cases and 92% of the controls (Table 5).

After matching by age and company, 38 matched sets of cases and controls were developed from the 44 cases and 134 controls. There are fewer matched sets than cases because, in six instances, it was necessary to combine cases of similar age within the same set in order to have at least one control per matched set. The Mantel-Haenszel procedure was used to derive a summary estimate of relative risk and to test for significant departures from unity (4, 7). In this procedure, each of the 38 sets can be viewed as a 2×2 contingency table. Thus, the ith set can be represented as in Table 6.

Relative risk is defined as the ratio of the probability of dying from cancer of the breast among women exposed to PVC to the probability for women not exposed. Estimates of these individual probabilities are not available from a case-control study. However, a measure of estimated relative risk from case-control studies as suggested by Mantel and Haenszel has been calculated as in Eq. (2). To assess whether the departure from unity of an observed relative risk is too great to have occurred by chance alone, a summary chi-square test corrected for continuity was performed using the Mantel-Haenszel procedure. The calculated chi-square must be 3.84 or larger in order to conclude with 95% assurance that the observed relative risk did not differ from unity by chance alone.

$$R = \Sigma_i (A_i D_i T_i)/\Sigma_i (B_i C_i/T_i) \qquad (2)$$

Combining the five exposure categories into two may be accomplished in a variety of ways, resulting in several possible relative risk measures as shown in Table 7.

None of the calculated relative risks, including the second shown which treats anything other than no exposure as definitely exposed, are statistically

Table 6. Representation of ith set.

	PVC exposure		
	Yes	No	Total
Cases	A_i	B_i	N_{1i}
Controls	C_i	D_i	N_{2i}
Total	M_{1i}	M_{2i}	T_i

significant; i.e., they may have occurred by chance alone. Similar analyses were carried out on a company-by-company basis. None of the relative risks so calculated is significantly different from unity.

Discussion and Summary

The cross-sectional mortality study was designed with two objectives. The first was to determine if any angiosarcoma deaths had occurred among employees of the PVC fabricators under study. Since no angiosarcoma deaths were found among the employees studied, the first question has an unequivocal answer. A secondary objective was that of examining the distribution of deaths by cause among the employees under study. Implicit in that objective is the question of whether or not that distribution is, in some sense, unusual. There is no unequivocal answer to the latter question. Whether or not an observed distribution of causes of death is unusual clearly relates to the standard or comparison population as well as the analytic methodology (*8*). This is illustrated by the observation that there are PMR's which are significantly different from unity on the 1968 standard and not on the 1964-1973 standard. However, it seems much more important to focus on the large area of agreement between the two standards rather than on the few areas of disagreement.

On the basis of the PMR analyses, there are statistically significant excesses in total cancer mortality among both white males and white females when compared to the distribution of deaths for the total United States specific for color and sex and adjusted for age. Excesses in cancer mortality appear concentrated in cancers of the digestive system and, in particular, in cancers of the intestine for both men and women. In addition, there is a suggestion that mortality from cancer of the breast and urinary organs among white women employees is higher than that for the total U.S. There are, however, several reasons why definitive interpretation is difficult. Factors meant to suggest that proportionate mortality analyses must be interpreted cautiously have been reviewed previously (*9-11*). However, while these results must be interpreted with caution, they appear to be consistent with previously studied workers and suggest the need for some continuing investigation (*1*).

One such follow-up investigation has been presented here in the form of a case-control study involving the 44 breast cancer deaths. On the basis of a case-control analysis, estimates of relative risk were derived but none of these relative risk estimates is significantly different from one, although such results must be interpreted with caution.

Absence of a statistically significant relative risk does not demonstrate that there is not an excess risk of death from breast cancer among women employees with PVC exposure. In fact, when no statistically significant relative risks are found, it is pertinent to ask what the chances are of detecting an increase of a given magnitude from the available data. Using the method described by Walter (*12*) we have subjected each of the relative risk estimates (Table 7) to a least significant relative risk analysis under the conditions that we desire 95% assurance that a risk of such magnitude, if observed, did not occur by chance alone and 80% probability of detecting the least significant relative risk if it exists.

Even in the case where all but no exposure are counted as exposed, the smallest relative risk which could be detected from these data is nearly 3:1. Nearly 200 cases and 200 controls would have been necessary to detect a true doubling of the risk under the specified conditions. Given the sample size in this study and the percentage of controls exposed (a percentage which was unknown at the

Table 7. Relative risk (RR) and least significant relative risk (LSRR) estimated for contrasts of various exposure category combinations.

Contrast	Number of cases	RR (Relative risk) estimate[a]	LSRR (Least significant relative risk) estimate[b]
Definite exposure vs. no exposure	29	1.81	6.77
Definite + improbable + possible + unknown exposure vs. no exposure	44	1.94	2.92
Definite + possible exposure vs. no + improbable exposure	35	0.624	5.02
Definite + possible + unknown exposure vs. no + improbable exposure	44	2.73	3.41

[a]None of the relative risk estimates are statistically significantly different from unity ($p > 0.05$).
[b]The true relative risk would have to be at least this large to have an 80% assurance of detection (i.e., power = 0.80) with a type I error of 0.05 (i.e., $\alpha = 0.05$).

...art of the study), it would be possible to detect ...ly very large increases in risk. There seems ...sonable assurance, therefore, that such very ...rge increases in the risk for breast cancer do not ...ist among these PVC fabricators, but no such ...tement can be made for possibly smaller increases ...risk.

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Mortality and Cancer Rates among Workers in the Swedish PVC Processing Industry

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Personnel lists from four PVC-processing industries were collected on production of employees with at least three months of employment at the beginning of 1945 and the last day of employment December 31, 1974. Of 2073 persons, 103 could not be followed up, because they had moved abroad. The remaining persons comprise the cohort of 1970 individuals who were analyzed and compared with the national population with respect to mortality from various diseases and cancer morbidity.

The death risk from myocardial infarction is elevated in the cohort. This elevation is most clearly apparent in the subcohort which had at least two years of exposure time and where the analysis was directed at circumstances chronologically close to the time of exposure. The myocardial infarction risk related to vinyl chloride exposure is discussed in relation to earlier studies on the vascular effects of vinyl chloride. An indication of an elevated risk of morbidity and mortality from tumors in the digestive organs is also present. However, this is not statistically confirmed. A few future follow-ups of the present study are necessary in order to clarify any possible elevated risk of tumors in the PVC-processing industry.

Vinyl chloride has been shown to cause scleroderma, Raynaud's phenomenon, acroosterolysis, liver damage and liver cancer (hemangiosarcoma) (*1*) in workers exposed to vinyl chloride monomer (VCM). This has been shown in studies (*2*, *3*) performed at companies which fabricate poly(vinyl chloride) (PVC). In animal experimental studies it has been reported that inhalation of VCM causes malignant tumors in different organs in rodents (*4-6*).

In Sweden, in 1974, two cases of liver hemangiosarcoma were diagnosed in employees at a company engaged in the processing of VCM and PVC (*7*). Later another two cases occurred at the same factory.

Studies on other forms of cancer (*8*, *9*) suggest that VCM-exposed workers in the PVC fabricating industries may possibly run an elevated risk of contracting forms of cancer other than hemangiosarcoma in the liver. Earlier, an excess mortality from cardiovascular diseases was also observed (*10*) in employees in the PVC manufacturing industry.

The present retrospective cohort study was performed for the purpose of determining the pattern of morbidity and mortality in the PVC processing industry. The PVC processing industry, generally speaking, has had a lower level of exposure to VCM than the fabrication industry. In the Swedish PVC processing industry, at present, about 5000 persons are employed in production.

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Material and Methods

Information for the study was collected from four PVC processing companies. The four companies all used PVC which, after additions of various chemicals, is heat-treated for fabrication into floor covering, lace, pipes, and food packaging.

Data Collection

The following data were collected from the personnel lists at the companies: personal number, name, beginning and end of exposure (year and month) and class of exposure.

In order for a person to be included in the original cohort, at least three months of employment was required in the period beginning in 1945 and the ending December 13, 1974. The exposure was classified as follows: class 3 (high), work in the mixing department; class 2 (medium), heat treatment machines; and class 1 (low), other production departments.

The collected data were transferred to punched cards and magnetic tape for statistical processing. The magnetic tape was coordinated with the national total population and the so-called death tapes for the 1961-1976 period and checked against the cancer registry by the Central Bureau of Statistics (SCB). The personnel numbers which could not be recovered at this time were checked by the national taxation office. The original cohort included a total of 2,073 persons. Of these, 103 persons (5%) dropped out, 70 or whom had moved abroad, 5 were found in the missing persons register of the tax office, and 28 could not be traced.

Study Cohorts

For the statistical processing, the results of the cohort of 1970 persons were divided into a number of subcohorts (study cohorts): (1) all persons with at least three months of exposure (follow-up time from the beginning of exposure and through 1976); (2) all persons with at least six months of exposure excluding those who stopped before 1961 (follow-up time from beginning of exposure but no earlier than 1961 and through 1976); (3) all persons with at least six months of exposure and where the exposure began no earlier than 1961 (follow-up time from beginning of exposure and through 1976); (4) all persons with at least two years exposure (follow-up time from two years after beginning of exposure but no earlier than 1961 and through 1976 but no more than ten years after exposure stopped); (5) all persons with at least two years exposure (follow-up time from ten years after exposure began but no earlier than 1961 and through 1976).

The two latter named study cohorts were chosen in order to study whether any differences existed in the death cause pattern with respect to when the deaths occurred after the beginning of exposure. The first of the study cohorts was intended to shed light on possible causes of death which occur relatively early, e.g., accidents caused by the job. The second was intended to shed light on such death causes as occurred after a longer time had passed. Tumors caused by occupational exposure, for example, often have a long latency period, 5-10 yr or longer.

Results

The original cohort was relatively young at the beginning of exposure. The age distribution in the different exposure classes is given in Table 1. One finds various dissimilarities between the exposure classes. In class 1 (low), 41.7% were younger than 35 years at the beginning of exposure; in class 2 (average), 47.7%; and in class 3 (high), 50.6%. There

Table 1. Age distribution in original cohort at beginning of exposure

Age	% in each exposure class			
	1	2	3	1-3
< 19	1.6	2.0	8.9	2.1
20–24	7.5	14.6	14.3	9.2
25–29	13.5	15.7	21.4	14.4
30–34	19.1	15.4	17.0	18.3
35–39	17.0	13.2	10.7	15.9
40–44	13.7	12.6	9.8	13.3
45–49	11.1	12.6	8.9	11.3
50–54	8.0	7.8	5.4	7.8
55–59	5.1	3.9	1.8	4.7
60–64	2.6	2.0	1.8	2.4
> 65	0.7	0.3	0.0	0.6
No. of persons	100% (1501)	100% (357)	100% (112)	100% (1970)

Table 2. Distribution of exposure time in the original cohort

Months	% in each exposure class			
	1	2	3	1-3
< 5	13.1	0.3	0.0	10.1
6–23	38.4	8.4	8.9	31.3
24–59	25.0	17.4	10.7	22.6
60–119	15.3	45.7	15.2	20.6
> 120	8.2	28.3	65.2	15.1
	100% (*M* = 1510)	100% (*M* = 357)	100% (*M* = 112)	100% (*M* = 1970)

Table 3. Observed and anticipated number of deaths as of December 31, 1976.

Cohort	Number	No. of deaths		Ratio O/E	Approx. 95% confidence interval
		Observed	Expected		
Exp. class 1	1303	53	55.5	0.95	± 0.26
Exp. class 2	356	14	21.9	0.64	± 0.34
Exp. class 3	112	6	10.3	0.70	± 0.47
Exp. class 1–3	1171	73	87.8	0.84	± 0.19

Table 4. Observed and anticipated number of deaths from certain causes during the 1969–1976 period in those with at least six months of exposure including those who stopped before 1961.[a]

	Observed	Expected	Ratio O/E
Malignant tumors 140–209	17	14.0	1.21
Respective organ tumors 150–159	8	4.9	1.63
Cerebrovascular diseases VII	22	24.3	0.91
Myocardial infarction 410.90	15	20.0	1.49
Accidents, suicide, etc. XVII	13	9.2	1.42

[a]Risk calculated from the beginning of exposure but no earlier than 1961. Study cohort 2 (1771 persons).

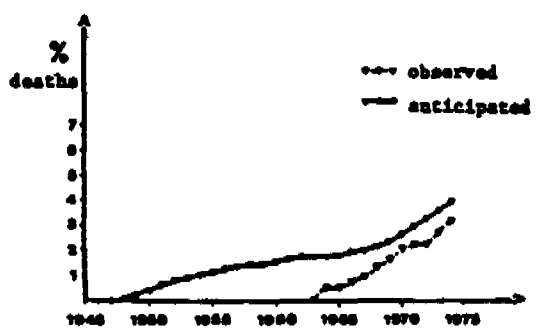

FIGURE 1. Cumulative deaths (in percent): (▽) observed; (▼) anticipated. Expected value calculated from beginning of exposure. Study cohort 1 (1970 persons). The percentage for a given year was calculated as 100 (number of persons dying through year in question divided by the number of persons beginning exposure up to and including the year in question).

were also dissimilarities in the length of exposure with respect to exposure class (Table 2). However, it should be noted that the table includes cases which were still under exposure at the final date for entrance into the cohort (December 31, 1974), for which reason, a certain bias toward short exposure times is found. Regardless of this, exposure class 3 has longer exposure times on the average.

The cohort as a whole reveals no noteworthy increase in the total risk compared with the national average, nor is there any indication of this in the subgroups making up the study cohort.

Study cohort 1, which includes everyone with at least six months of exposure and with calculation of the risk from the beginning of exposure, is somewhat remarkable in that the anticipated number of deaths is significantly higher than that observed up to 1964 (Fig. 1). This is commented on further in the discussion. Study cohort 2 (Tables 3 and 4; Fig. 2) includes persons with at least six months of exposure, excluding those who stopped before 1961. The risk calculation is made from the beginning of the exposure, but no earlier than 1961 and up to the end of the follow-up time (1976). The observed number of deaths is somewhat lower than expected, much lower in exposure class 2. Classes 2 and 3 are relatively small and are sensitive to random deviations in this type of analysis. In order for random deviations not to influence the results, the classes were combined. This is true of all study cohorts. This distribution with respect to the vari-

Table 5. Observed and anticipated number of deaths as of December 31, 1976 in those with at least six months of exposure beginning no earlier than 1961.[a]

Cohort	Number	No. of deaths		Ratio O/E	Approx. 95% confidence interval
		Observed	Expected		
Exp. class 1	1139	43	41.2	1.04	± 0.31
Exp. class 2	247	4	11.7	0.34	± 0.34
Exp. class 3	42	1	1.8		
Exp. class 1–3	1428	48	54.7	0.88	± 0.35

[a]Risk calculation from beginning of exposure. Study cohort 3 (1428 persons).

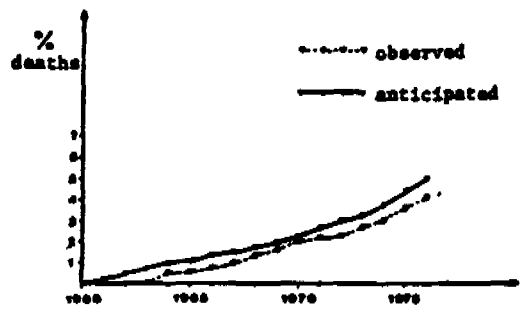

FIGURE 2. Cumulative deaths (in percent). Expected value calculated through 1961. Study cohort 2 (1771 persons). Percentage for a given year calculated as in Fig. 1.

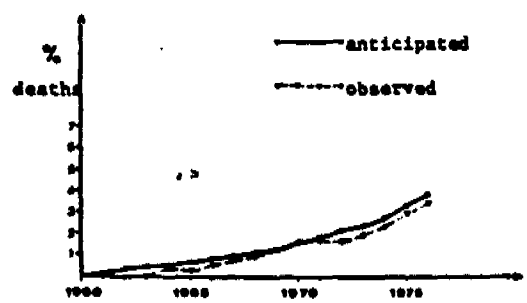

FIGURE 3. Cumulative deaths (in percent) of those who began exposure in 1960 or later. Study cohort 3 (1428 persons). Percentage for a given year calculated as in Fig. 1.

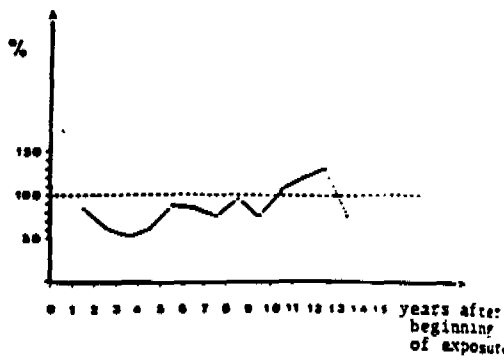

FIGURE 4. Observed death risk per year at different points of time after beginning of exposure expressed in percent of corresponding anticipated risk in those who began exposure in 1961 or later. Study cohort 3 (1428 persons).

Table 6. Observed and anticipated number of deaths from certain causes during the 1969–1976 among those with at least six months of exposure beginning in 1961 or later.[a]

	Observed	Expected	Ratio O/E
Malignant tumors 140–209	9	9.7	0.93
Digestive organ tumors 150–159	4	3.3	1.20
Cardiovascular diseases VII	16	16.2	0.99
Myocardial infarction 410.90	14	11.2	1.25
Accidents, suicide, etc. XVII	11	7.3	1.51

[a]Risk calculated from the beginning of exposure. Study cohort 3 (1428 persons).

ous death causes is shown in Table 4. The observed and anticipated number of deaths during the 1961-1968 period is relatively small, only a few cases, and the death cause classification was modified as mentioned earlier in 1969, for which reason 1961-1968 period is not discussed separately. By and large, the picture is the same there as for the 1969-1976 period reported on. From Table 4, one sees that the observed number of deaths, especially those from tumors of the digestive tract, myocardial infarction and accidents, is somewhat higher than anticipated. However, the differences are not significant. Study cohort 3 (Tables 5 and 6; Figs. 3-5) which pertains to those who began working in 1961 or later but which otherwise satisfy the same criteria as study cohort 2, displays a similar picture.

An analysis of study cohort 3 according to formula B (Figs. 4 and 5) indicates that the annual risk during the first year of exposure is somewhat lower than the anticipated one, but that after about ten years, an increased risk occurs so that the observed risk becomes higher than the anticipated.

Table 7. Observed and anticipated number of deaths from certain causes during the 1969–1976 among those with at least two years of exposure.[a]

	Observed	Expected	Ratio O/E
Malignant tumors 140–209	5 (9)	7.4 (8.9)	0.86[b] (1.01)
Digestive organ tumors 150–159	2 (4)	2.6 (3.2)	0.78[b] (1.27)
Cardiovascular diseases VII	15 (16)	12.7 (15.8)	1.18[b] (1.01)
Myocardial infarction 410.90	11 (12)	5.4 (6.6)	2.03[b] (1.82)[b]
Accidents, suicide, etc. XVII	4 (5)	4.6 (5.1)	0.87[b] (0.97)

[a]Risk calculated from two years after beginning of exposure and no more than five years (10 years) after end of exposure. Study cohort 4 (1155 persons).
[b]$p < 0.05$.

Table 8. Observed and anticipated number of deaths from certain causes during the 1969–1976 in those with at least two years of exposure.[a]

	Observed	Expected	Ratio O/E
Malignant tumors 140–209	9	6.0	1.51
Digestive organ tumors 150–159	4	2.2	1.85
Cardiovascular diseases VII	12	11.1	1.08
Myocardial infarction 410.90	8	4.5	1.77
Accidents, suicide, etc. XVII	2	2.5	0.79

[a]Risk calculated from 10 years after beginning of exposure. Study cohort 5 (680 persons).

Table 9. Observed and anticipated number of deaths from cancer during 1961–1976 in those with at least six months of exposure excluding those who stopped before 1961.[a]

	Observed	Expected	Ratio O/E
Malignant tumors (total)	51	44.6	1.14
Digestive organ tumors (150–159)	11	8.5	1.29

[a]Risk calculated from beginning of exposure but no earlier than 1961. Study cohort 2 (1771 persons).

In study cohort 4 (Table 7) which concerns time during ongoing exposure or a relatively short time after the end of exposure, i.e., "short-term perspective," one sees an increased death risk from myocardial infarction. Other causes are somewhat lower here than expected.

In study cohort 5 (Table 8), finally, one finds an indication of an increase in the death risk as regards tumors, but also for myocardial infarction. The differences between the observed and anticipated numbers are not, however, statistically confirmed at the 5% level.

The result with respect to mortality can be summarized as follows. In the study cohorts, overall, one finds no noticeable increase in mortality. On the other hand, there are indications of a shift in the death cause pattern compared with the national average. This shift is expressed primarily in the fact that the number of myocardial infarctions is noticeably higher during ongoing exposure or within a relatively short period of time after the end of exposure. There are also indications that the death from tumors can be elevated among persons with a long latency period (Tables 7 and 8).

In the question of cancer morbidity, there is no certain increase in study cohort 2 (Table 9 and Fig. 6). In the question of tumors of the digestive organs, in the same study cohort, 11 cases were observed as opposed to an anticipated 8.5. The difference is not statistically verified. One of these eleven tumors was liver cancer (ICD 155.0).

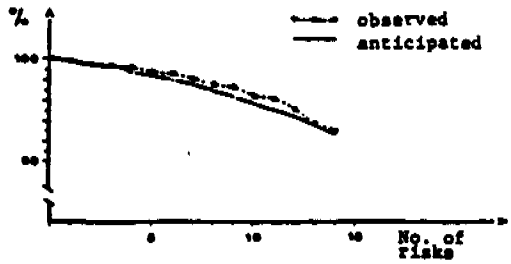

FIGURE 5. Cumulative survival probability (in percent) of those who began exposure in 1961 or later and have at least six months of exposure. Study cohort 3 (1428 persons).

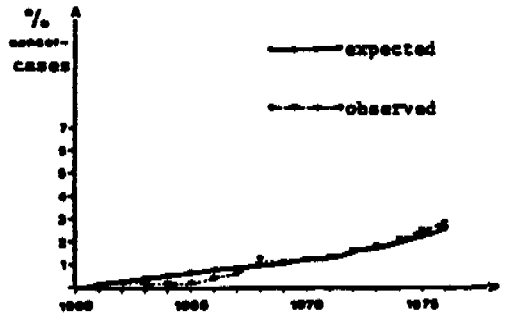

FIGURE 6. Cumulative rates of cases of all cancer (in percent). Study cohort 2 (1771 persons). The percentage for a given year was calculated as 100 (number of persons diagnosed through year in question divided by the number of persons beginning exposure through year in question).

Discussion

A noteworthy finding which arises in the analysis of the total cohort mortality (Fig. 1) is that the number of deaths at the beginning of the observation period (1947-1964) is significantly lower than one would expect in relation to the national average. This difference is so great that one cannot directly consider it to be randomly conditioned, nor can it be entirely ascribed to the so-called healthy worker effect. Theoretically, of course, the possibility exists that the selected cohort, in the question of mortality and the factors which influence said mortality, deviates from the general population. A more credible possibility is, however, that the personnel register that was available at the company involved at the time of this study was incomplete in the matter of hirings during this early period. A personnel register which, in the mid-1960's, was purged

of persons who began employment before 1960, could lead to the difference mentioned above. The companies involved reported that such a purging did not occur, so far as they knew.

If such a purging (thinning out) nevertheless occurred, this would have resulted in the elimination of persons with a long observation time at the time of follow-up. In the present study, the risk calculations were limited to beginning no earlier than 1961. This means a limitation of the analysis to pertain to the group of employees who were living at the beginning of 1961 and where the risk of an elimination is positively eliminated. This limitation, however, signifies a weakening of the analysis, since parts of the cohort with long follow-up times are excluded. Basically, this weakening signifies a poorer possibility of discovering an elevated incidence of cancer if one exists.

The myocardial infarction mortality (ICD 410.90) is elevated in the cohort. This elevation occurs most clearly in the category of the total cohort which has at least two years of employment time and where the analysis was directed at the period of time following two years after the beginning of employment and extending to no more than five years after the beginning of employment. Therefore, this involves that fraction of the mortality from myocardial infarction which chronologically is relatively closely connected to the time of employment. It is impossible on the basis of such observations to draw conclusions that the elevation was caused by exposure to vinyl chloride. The observed increase in myocardial infarction mortality is, however, so striking that it, in combination with the known facts about the toxic properties of vinyl chloride, must be given consideration. There are no reasons to assume that varying diagnostics, standards or practices in filling out the death certificates alone could provide an explanation. A natural conclusion is, therefore, that if one disregards the possibility of a random local phenomenon, the increased frequency is to be ascribed either to selection of individuals susceptible to the risk or an outbreak of risk factors in the close environment of employees. A combination of these two circumstances is, of course, also possible theoretically.

In this connection, it should be noted that many risk factors for myocardial infarction are environmentally conditioned in the fact that they constitute part of the lifestyle of the modern social environment in an industrialized country. Cigarette smoking, physical inactivity, overweight and high blood lipids constitute environmental factors which are related to social behavior. It is a well known fact that the risk of coronary vascular disease in the heart varies, inter alia, with the total load of risk factors. Among other risk factors, one can also name hereditary characteristics and high blood pressure. In this connection, there is reason to recollect that the causal network of coronary disease is multifactorial and that the disease has an environmental relationship in the broad sense. There is also reason to recall the aspect that the total risk increases when several risk factors, known or unknown, are allowed to collaborate (*11*, *12*).

It has not been possible to establish the distribution of such already known risk factors for coronary disease in the cohorts studied with respect to the national population in general. Therefore, no continued analysis of the matter of the causal relationship between close environment and heart disease morbidity can be made within the limits of the study.

Exposure classes 2 and 3 constitute subcohorts that are too small, in the present study, to allow a meaningful discussion of the myocardial infarction risks relative to the various exposure levels in the processing industry. In this connection, one should also consider the circumstance that the exposure classes in this study are based on interviews with the employees directed at the work environment at the time in question some 10 to 15 years ago. Therefore, this involves an environment which has subsequently undergone changes. Objective classification criteria in the matter of exposure, e.g., in the form of environmental measurements, do not exist. The distribution into exposure classes is, for this reason, fraught with uncertainty.

In animal experiments, it has been found that the toxicity picture in rodents chronically exposed to VCM involves the blood vessels. Besides hemangiosarcoma in the liver and the other organs (*4*, *5*) the inhalation of VCM is also believed to cause development of telangiectasis (*4*) in the liver of mice which can lead to death from hemocoele. Changes in the sinus cells have been observed in liver biopsies in VCM-exposed workers (*13*). Capillary changes in the skin of the fingers have also been observed (*14-16*), both in VCM-exposed workers with other vascular-involved diseases, such as acroosteolysis, Raynaud's phenomenon, and sclerodermia, and in VCM-exposed workers without such diseases. An over-representation of deaths from cardiovascular diseases has also been observed in a study on the PVC-fabricating industries (*10*). Animal experimental and previous medical studies of VCM-exposed populations therefore support the assumption that the increased risk of myocardial infarction observed in the present study could possibly be ascribed to VCM exposure.

As regards the mortality and morbidity from tumors, the results are uncertain. There are certain

...dications of an elevation, but the differences are ... statistically confirmed. One can think of two ...sibilities here: (1) in reality, there is no increase ... the risk of tumors; (2) there is indeed an in...ased risk of tumors. The results neither confirm ... refute this. Tumors do not occur until after a ... latency period. The majority of the persons ...cluded in the study did not begin their exposure ...til the 60's and 70's and therefore could not be ...llowed for a sufficiently long time. An accurate ...llow-up of the present cohort during the coming ...e-year period should bring greater clarity into ...is.

In the present connection, it is of interest that in a recently published mortality study (*17*) on almost ... deaths in the American PVC-processing in...stry, an overrepresentation in cancer mortality ...pears to exist (all cancer), especially gastrointes...inal cancer in both sexes.

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Epidemiological Study of Pneumoconiosis in the Italian Poly(vinyl chloride) Industry

by G. Mastrangelo,* B. Saia,* G. Marcer* and G. Piazza†

Among 1216 workers employed in a poly(vinyl chloride) production factory, 20 cases of pneumoconiosis were found. None of these workers had had previous exposure to organic or inorganic dusts; 731 had been exposed to PVC dust (employed in drying, sacking and blending of polymer) and 485 had been exposed to monomer alone. Chest x-ray films were read by two independent physicians utilizing the ILO/UC Pneumoconiosis Classification, 1971. X-ray abnormalities were characterized by limited profusion, irregular type and low gravity; in a small percentage of cases these were associated with slight restrictive respiratory function impairments. All 20 workers with PVC-induced pneumoconiosis had been exposed to high PVC dust pollution for at least five years. Mild nonspecific alterations (profusion of 0/1 class) were found both in the group exposed to PVC dust and in the group exposed to VCM alone. Such changes (observed in 388 cases, 31.9% of the whole population), are related mainly to age and smoking habits, and the role of exposure is minor.

We examined the working population of plants producing poly(vinyl chloride) (PVC) in Porto Marghera, Italy; 1216 workers had no previous dust exposure. Of these 731 were exposed to PVC dust polymer alone while 485 were exposed to vinyl chloride monomer (VCM). In the drying, sacking and blending departments, PVC dust concentrations were over 10 mg/m^3 of total dust in about 60% of the samples, whereas in the polymerization departments no concentration over 10 mg/m^3 was found. In the samples taken, particles with diameters of 1 μm to 6 μm constituted 4.5 to 30.9% of total dust weight.

All the workers had chest x-rays according to ILO standards and a spirographic examination. Chest x-ray films were read by two independent physicians utilizing the ILO/UC pneumoconiosis classification. For statistical analysis, a consensus reading was used.

Table 1 shows that there are no significant differences in age and smoking habits, but the exposure duration is higher in the workers not exposed to dust.

Table 1.

Group	No. of subjects	% of smokers	Age, yr (mean ± SD)	Exposure, yr (mean ± SD)
Exposed to PVC dust	731	73.9	37.7 ± 8.8	6.1 ± 4.0
Not exposed to PVC dust	485	68.7	35.7 ± 8.5	8.6 ± 4.5

Table 2.

PVC dust exposure, yr	Age distribution of cases[a]			
	≤ 30 yr	31–40 yr	41–50 yr	> 50 yr
< 5	-	-	-	-
5–10	-	2(2.4)	5(8.3)	1(5.9)
> 10	-	2(3.8)	8(9.0)	2(9.5)

[a]Values in parentheses are percentages of subjects with PVC pneumoconiosis in each class of age and exposure.

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In 20 subjects we found chest x-ray changes of at least class 1 according to the ILO/UC classification. The mean age of this group was 44.9 ± 5.2 years and the mean length of exposure was 11.6 ± 5.4 years. Sixteen subjects (80%) were either smokers or ex-smokers.

Table 2 summarizes the distribution of cases in relation to age and length of exposure. In all age groups there is an increase of disease prevalence associated with the increasing length of exposure.

In the case of the x-ray changes, 16 subjects had class 1/0 profusion, 2 cases class 1/1, 1 case class 2/1, and 1 case class 2/2. Irregular opacities were prevalent: 10 were type s, three were type t, six were type p and one was type r. They were diffused, mainly over median lobe areas.

A chest x-ray of a worker exposed to PVC dust (Fig. 1) for 15 years shows a gross reticular pattern: profusion is class 2/2, type t. In the right hemithorax of the same subject (Fig. 2) there is a mottled reticular pattern. Figure 3 is an enhanced view of the right hemithorax showing the mottled reticular pattern more clearly.

Another case of PVC induced pneumoconiosis can be seen in Figure 4. The worker was exposed to PVC dust for 20 years. A fine, dense reticular micronodulation is evidenced. Profusion is class 2; type p-s. Figure 5 shows the right hemithorax of the same subject; pin-point opacities can be seen.

In spite of age and the considerable exposure, the majority of cases were in a low profusion category, indicating the slow evolution of the disease. All had worked in high air-borne dust level environments (mostly drying and sacking) for at least five years. None of the 20 subjects was in a group unexposed to dust and none had experienced previous occupational exposure to organic or inorganic dusts. We considered the alterations to be PVC pneumoconiosis.

In 388 subjects (31.9%) we found slight chest x-ray alterations consisting of linear or irregular vanishing opacities or both, classified as class 0/1; the remaining 808 subjects were class 0/0.

Table 3 reports the total population distribution excluding 20 subjects with PVC pneumoconiosis. Results are presented in a two-way table: each entry reports the number of observations. Samples are classified according to age and PVC dust exposure: PVC + represents presence, and PVC - absence of PVC; x-ray + indicates the group with

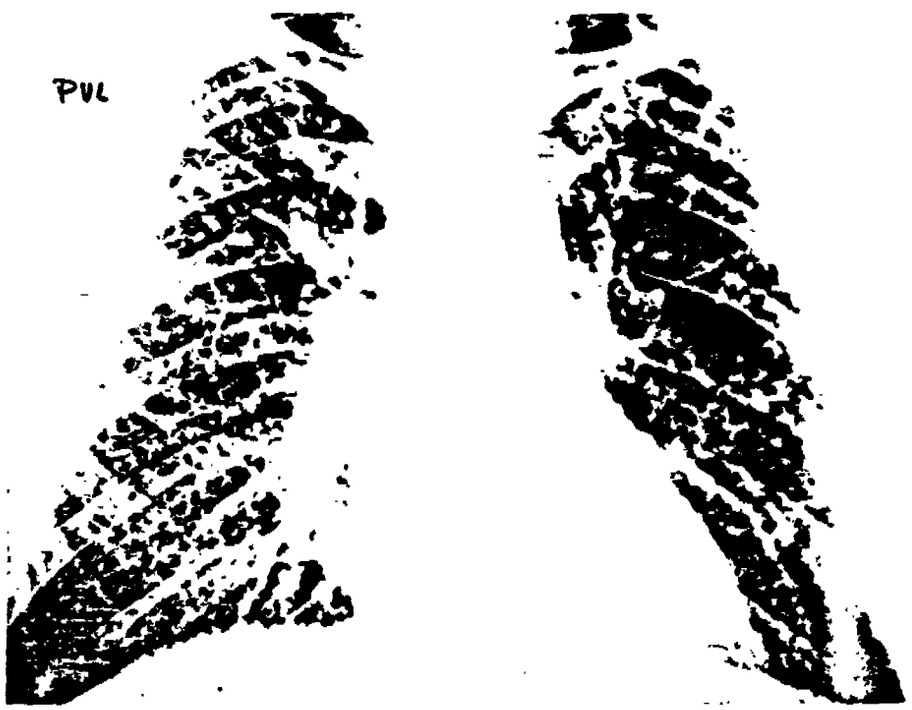

FIGURE 1. Chest x-ray of a worker exposed to PVC dust for 15 years. Profusion class 2/2; type t.

FIGURE 2. Right hemithorax of the same subject as in Fig. 1.

FIGURE 3. Enhanced view of the right hemithorax of Fig. 2, showing the mottled reticular pattern.

class 0/1 profusion. To assess the influence of both risk indicators we performed a two-way analysis of variance for proportions.

Table 4 shows that both age and exposure were significant factors influencing x-ray abnormalities. The square of a multiple partial association coefficient for qualitative data was calculated to measure the degree of association between the dependent variable (x-ray changes) and each of the two predictor variables (age and exposure). Age and exposure are alternately held constant. Age is a most important factor. When exposure is held constant, 33.2% of the x-ray changes are shown to depend upon age, when age is held constant, 6.5% are shown to depend upon exposure.

Table 5 summarizes the distribution of the cases according to smoking habits in workers exposed and not exposed to PVC dust.

Table 6 shows that chest abnormalities are significantly influenced by both risk indicators.

Table 3.

	Age distribution of subjects			
	≤ 30 yr	31–40 yr	41–50 yr	> 50 yr
PVC +				
X-ray +	20	78	123	35
X-ray −	133	197	108	17
PVC −				
X-ray +	17	45	55	15
X-ray −	119	158	67	9

Table 4.

Source of variation	Degrees of freedom	Sum of squares	Mean squares	F
Age	3	30.9713	10.3238	53.81[a]
PVC dust exposure	1	0.7843	0.7843	4.09[b]
Interaction	3	0.9882	0.3294	1.72
Error	1188	227.9403	0.1919	

[a] $p < 0.01$.
[b] $p < 0.05$.

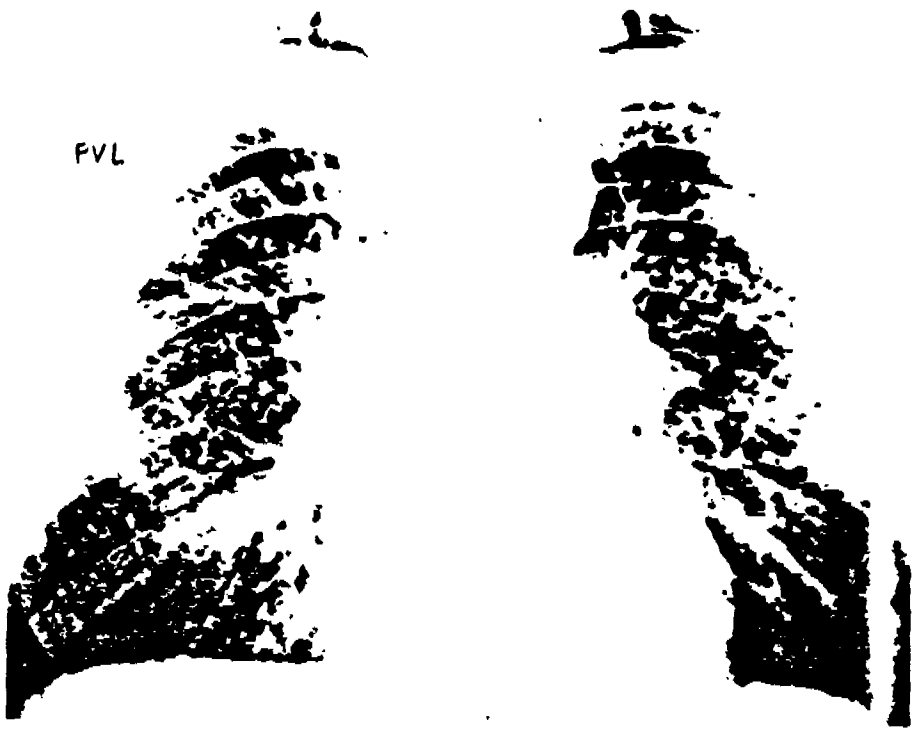

FIGURE 4. Chest x-ray of a worker exposed to PVC dust for 20 years. Profusion class 2/1; type p-s.

Table 5.

	Nonsmokers	Smokers
PVC +		
X-ray +	40	216
X-ray −	147	308
PVC −		
X-ray +	25	107
X-ray −	127	226

Table 6.

Source of Variation	Degrees of freedom	Sum of squares	Mean squares	F
Age	1	7.8850	7.8850	37.31[a]
PVC dust exposure	1	1.7847	1.7847	8.44[a]
Interaction	1	0.1023	0.1023	1.0
Error	1192	251.9125	0.2113	

[a] $p < 0.01$.

FIGURE 5. Right hemithorax of the same subject as in Fig. 4

When exposure is held constant, habitual smoking is responsible for 17.1% of the changes. When smoking habits are held constant, exposure to PVC dust is shown to be responsible for 8.9% of the x-ray abnormalities.

Our epidemiological study confirms experimental and pathological data already reported regarding the effects of PVC dust. Lung changes are directly related to PVC dust exposure, whereas VCM exposure alone fails to cause these changes. Therefore, we believe that pulmonary changes are not pathogenically similar to other vinyl chloride induced abnormalities, that is fibrosis of the liver, scleroderma-like skin changes, and peripheral vascular damage.

In our study there was only a 1.6% prevalence of pneumoconiosis in the total population, but in the workers exposed to effective risk of pneumoconiosis (731 subjects) the prevalence rose to 2.7%.

Apart from 20 cases of pneumoconiosis, mild nonspecific alterations (profusion of 0/1 class) were found in the group exposed to PVC dust and in the group exposed to VCM alone. Such changes are related mainly to age and smoking habits, and the role of exposure is minor.

as in Fig. 4.

tives

Excess Lung Cancer Risk in a Synthetic Chemicals Plant

by Richard J. Waxweiler,* Allan H. Smith,† Henry Falk‡ and Herman A. Tyroler**

A standardized mortality ratio of 1.49 for respiratory system cancer (42 observed deaths versus 28.2 expected, $p < 0.01$) was observed among a cohort of 4806 males employed at a synthetic chemicals plant since its startup in 1942. Upon review of pathologic material, the excess was found to be limited to adenocarcinoma and large cell undifferentiated lung cancer. Many of the workers had been exposed to vinyl chloride, as well as to chlorinated solvents, poly(vinyl chloride) (PVC) dust, acrylates and acrylonitrile. To evaluate the association between lung cancer and occupational chemical exposures, detailed work histories for each cohort member were combined with exposure ratings for each of 19 chemicals for each job for each calendar year since 1942. A serially additive expected dose model was then constructed which compared the doses of the chemicals observed for the lung cancer cases to the doses expected based on subcohorts without lung cancer individually matched to the cases. PVC dust appeared to be the most likely etiologic agent ($p = 0.037$). Time trends of PVC dust exposure indicated a potential latent period of 5-16 years before death.

Introduction

Our previously published (*1*) retrospective cohort mortality study of workers exposed to vinyl chloride monomer (VCM) at a synthetic chemicals plant demonstrated an excess risk of death from respiratory system cancer in addition to the already recognized association between VCM exposure and angiosarcoma of the liver (*2-10*). Preliminary review of the lung cancer cases indicated they were all adenocarcinomas or large cell undifferentiated tumors—an unusual histologic distribution.

Although lung tumors have been induced experimentally by exposure to VCM (*2*), the epidemiologic data are suggestive but equivocal. Two cohort studies found no excess lung cancer risk (*4-6*). In six other studies, elevated lung cancer risks were found overall or among subcohorts; however, few of these excesses were statistically significant due to moderate excess risks and/or small numbers of cases (*7-9, 11-13*).

Because of the uncertainty in the literature regarding the association between VCM exposure and lung cancer and because of the diversity of occupational chemical exposures experienced by the lung cancer cases in our previous study (*1*), we decided to evaluate our cohort further to determine whether or not lung cancer was associated with VCM or with other chemical exposures. Thus, the following research had three objectives: (1) by using a retrospective cohort design, to determine if our previously published excess lung cancer risk among employees exposed to VCM at this synthetic plastics plant also existed for the total plant population (2) by using a case-comparand study, to determine whether an excess lung cancer risk of a particular histologic type was in force at the plant and (3) by using a serially additive expected dose model, to test whether one or more particular

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chemicals used at the plant were associated with either the excess risk of all or of a specific histologic type of lung cancer.

Methods and Results

Retrospective Cohort Study

The population at risk for the retrospective cohort study consisted of the 4806 males ever employed at this plant from its opening in 1942 until December 31, 1973. In the absence of individual data on race, everyone was assumed to be white because the company indicated that less than 2% of the population had been nonwhite. Date of birth and detailed work histories at this plant of all jobs and dates worked by each individual were coded. By follow-up of all study members from the first date hired at the plant through December 31, 1973, it was determined that 4174 were alive and 559 had died. The 73 (1.5%) persons lost to follow-up were considered alive throughout the study. The 16 (3%) deceased persons for whom no death certificates could be located were assumed dead, cause of death unknown. A modified life table analysis (NIOSH) was used to obtain person years at risk of dying by five year age and calendar time periods. United States white male death rates specific for five year age and calendar intervals were used to calculate the expected deaths and standardized mortality ratios (SMR's). SMR's were tested for statistical significance using the Poisson distribution (one-sided).

The cohort was young; by December 31, 1973, only 30% of the cohort, if alive, would have been over 54 years of age. However, 63% of the cohort had been hired before 1954 and thus had the opportunity to achieve 20 years' latency.

Two separate analyses of the cohort were made. Initially, all members were considered at risk from their first date of employment at the plant. This analysis yielded 556 observed and 550 expected deaths (Table 1). Risk of death due to malignant neoplasms of the central nervous system (SMR = 209) and respiratory system (SMR = 149) were both significantly elevated. A second "over ten-year latency" analysis was carried out by beginning person-years at risk only after an individual had achieved the tenth anniversary of his first date of employment at the plant. Results similar to those in the first cohort analysis were found but with slightly higher SMR's. Respiratory system cancer had an SMR of 156 based on 39 observed cases. Because our previously published analysis (*1*) of just the presumably VCM-exposed workers at this plant also found an SMR of 156 after 10 years latency, these results indicate an excess lung cancer risk not solely due to VCM exposure.

Table 1. Observed and expected deaths among chemical plant worker cohort.

Cause (ICDA–7 Code)	Observed	Expected	SMR
All causes	556[a]	550.2	101
All malignant neoplasms (140–205)	109	92.5	118
Digestive system (150–159)	24	25.6	94
Respiratory system (160–164)	42	28.2	149[c]
Central nervous system (193)	9	4.3	209[c]
Lymphatic and hematologic (200-205)	9	11.4	79
Other cancers	25	23.0	109

[a]Five persons, including three of the original 559 deaths, were not included in the cohort analysis because of missing work histories.
[b]$p < 0.01$.
[c]$p < 0.05$.

Case-Comparand Study

The second objective of this study was to determine whether an excess risk existed for a particular histologic type of lung cancer. Because no historical data exist on histology-specific lung cancer incidence or mortality rates and because histologic classification is somewhat variable between pathologists and over time, a case-comparand design was chosen to accomplish the second objective.

Medical records and pathology reports were obtained on all deceased members of the cohort whose death certificates mentioned cancer or respiratory disease. For 45 cohort members, primary or unspecified lung cancer was reported on at least one of these three records. A few persons who died after December 31, 1973, the cohort ending date, were included. Of the 45 cases, 42 were born in Kentucky or an adjacent state. Histologic material was requested. The worker case group consisted of the 27 of the 45 deceased individuals for whom histologic specimens were available.

As a comparison group, the lung cancer cases (comparands) most closely preceding and succeeding the chemical plant worker case in the chronologically ordered hospital pathology logs were selected that matched in age at diagnosis, sex, race, and county of residence. For four cases, only one matched comparand could be found.

Histologic material was reviewed by a panel of pathologists unaware of the employment histories (case versus comparand status) of the deceased. The histologic type distributions, according to the

...erans' Administration classification scheme (*14*), ... compared between the cases and comparands.

The results of the majority opinion of the pathol... panel are listed in Table 2. The panel found a ...ficantly ($p < 0.05$, chi-square) higher percent... of large cell undifferentiated (type 4) cancers ... the worker cases than among the community ...parands (30% vs. 10%).

... using the SMR for respiratory system cancer ... 149 in the retrospective cohort study and the ...ved and expected histologic distribution of ... cancer deaths based on the case-comparand ... Table 3 demonstrates the calculation of his... specific lung cancer SMR's (column C). If the ... cases for which histologic specimens were avail... are considered representative of all 45 lung ...er cases, it appears the excess lung cancer risk ...ears limited to types 3 and 4, adenocarcinoma ... large cell undifferentiated, with the greater ... due to the latter. Approximately 13.5 of the ... excess lung cancers among the plant workers ...uld be due to adenocarcinoma and large cell ...differentiated carcinoma.[a,b]

... appears that there is a histology-specific ex... lung cancer risk among workers at this plant ... that this differential distribution of cell types is not an artifact of the geographic region nor of the pathologist's techniques. The fact that this risk occurs for adenocarcinomas and for large cell undifferentiated lung cancers makes it very unlikely that it is due to cigarette smoking.

Table 2. Case and matched comparand histologic distributions.

Histologic type	Veterans Administration classification code	Frequency: Worker cases	Frequency: Community comparand cases
Epidermoid	1	6 (22%)	15 (30%)
Small cell undifferentiated	2	6 (22%)	15 (30%)
Adenocarcinoma	3	7 (26%)	14 (28%)
Large cell undifferentiated	4	8 (30%)	5 (10%)
Other	–	0	1 (2%)
Total		27 (100%)	50 (100%)

Serially Additive Expected Dose Model

The third objective was to test whether any presumed occupational chemical exposures were associated with the excess lung cancer risk at the plant. It was decided to analyze the previously mentioned cohort data in a serially additive expected dose (SAED) model (*10*), obtaining for each lung cancer case the observed and expected doses of each chemical, conditional on certain characteristics. The purpose of the SAED model is to compare the observed exposure of each case in a study with the exposures of fellow workers close to the case in year of birth, and in age at commencement of work at the company. If the total work force in the plant under study is referred to as the cohort, then each case can be thought of as belonging to a subcohort of workers with approximately the same year of birth and age at commencement of work in the plant. In each year that a case worked at the plant, his exposure can be compared with that of the other members of his subcohort who were working in that year.

Company personnel compiled estimated exposures on a scale of 0 to 5 (5 being the highest exposure) for each of 19 chemicals (Table 4). Each job was assigned an exposure rank for each calendar year of the study (Table 5). These exposure data were then linked with work histories identifying the jobs each worker had in the plant and the calendar time involved. The analytical method is based on estimating exposure dose by multiplying the exposure level by the number of days worked at that level. These "doses" are accumulated over a calendar year for a case to yield the observed dose and for

Table 3. Histologic specific lung cancer risk among plant personnel.

	Histologic distribution: Observed (*A*)	Histologic distribution: Expected (*B*)	Histologic specific SMR $C = 149\ (A/B)$	Excess cases among those pathologically reviewed (*D*)[a]	Total excess cases (*E*)[b]
Total	100%	98%[c]	149	8.9[c]	14.8[c]
Epidermoid	22.2%	30%	110	0.6	0.9
Small cell	22.2%	30%	110	0.6	0.9
Adenocarcinoma	25.9%	28%	138	1.9	3.2
Large cell	29.6%	10%	441	6.2	10.3

[a] $D = (27\ A) - (27\ B \times 100/149)$.
[b] $E = (45\ A) - (45\ B \times 100/149)$.
[c] Specific cell types do not add up to total because of "other" type lung cancer among comparands.

his subcohort to yield an expected dose for each year that a case works. The methodology has previously been described in detail elsewhere (*10*).

In addition to testing the total-dose hypothesis, the SAED analysis facilitates examination of the observed and expected doses for each year of exposure before death. Exposures to 19 chemicals were assessed; seven of the chemicals were, however, excluded from the formal analysis because so few persons were exposed to them at levels 3, 4 and 5 (Table 6).

The SAED model analysis resulted in the observed minus expected cumulative dose differences per case in Table 7. The differences for PVC dust are striking in comparison with the other exposures. For the large cell undifferentiated cancer and adenocarcinomas combined and for large cell undifferentiated cancer by itself, the differences in exposure to PVC dust are three to four times as large as those estimated for vinylidene chloride, the

Table 4. Exposure ratings used to classify jobs.

Rating	Exposure
0	No exposure
1	Minimal exposure to low levels (chemical in building—not handled, low vapor pressure and dust level, probably works on different floor)
2	Moderate exposure (works around the chemical, but exposure is minimal)
3	Works in areas where subject to occasional high excursions (normally exposure is minimal but occasional spills, leaks, or dust exposure may occur)
4	Works in areas where level is high (exposure levels in the area are frequently high; might consider that some risk is involved if chemical is very toxic)
5	Intimate contact, skin or high inhalation (such as poly cleaners in earlier years handling slurry)

Table 5. Chemical exposure ratings specific for job identification number and calendar year for a given chemical.

Chemical #1, job identification number	Exposure ratings					
	1942	1943	1944	1945	1946	1973
1	0	0	0	2	2	2
2	5	5	5	5	5	5
3	2	2	1	1	0	0
.	.	.	.	.	.	.
.	.	.	.	.	.	.
.	.	.	.	.	.	.
84	4	4	4	1	1	1

Table 6. Frequency of job categories having at least one year of exposure greater than specific exposures levels.[a]

	No. at each exposure level				
	1	2	3	4	5
Acrylic acid	13	4	3	0	0
Acrylamides	14	4	4	0	0
Acrylonitrile	35	25	13	6	1
Acetylene	20	17	10	3	1
Acrylates	39	30	21	8	2
Bisphenol A	7	2	0	0	0
Butadiene	23	15	9	5	1
Caprylyl chloride	25	9	6	6	3
Chlorinated solvents	30	18	7	4	4
Chloroethyl vinyl ether	22	6	4	1	0
Diethyl maleate	14	6	0	0	0
Mercuric chloride	15	7	5	3	3
Methanol	30	21	14	2	2
Phenol	2	1	0	0	0
Toluene	2	0	0	0	0
Vinyl chloride	55	40	29	21	4
Vinylidene chloride	20	14	8	5	2
Vinyl acetate	26	18	10	0	0
PVC dust	56	32	19	9	6

[a]E.g., for acrylic acid, employees could have worked in 13 different job categories that had exposure levels of one or higher in at least one calendar year between 1942 and 1973.

Table 7. Observed minus expected cumulative dose differences per lung cancer case.

Chemical	All lung cancers	Pathologically reviewed cases	Adenocarcinoma and large cell	Large cell
Acrylonitrile	-652	-402	-446	-128
Acetylene	-353	-289	291	-167
Acrylates	-322	-251	-83	-339
Butadiene	-330	-207	-406	-622
Caprylyl chloride	-547	-258	-270	-1139
Chlorinated solvents	-868	-672	-150	749
Mercuric chloride	-507	-425	-211	-62
Methanol	-430	-618	-456	-1078
Vinyl chloride monomer	-1428	-795	26	907
Vinylidene chloride	-341	210	804	1525
Vinyl acetate	-707	-480	-217	328
PVC dust	768	2448	3225	4526

next most evident chemical. The significance levels of the larger of these differences are found in Table 8 for the total cumulative doses and also for cumulative doses until 10 years before death. Statistical significance was observed only for exposure to PVC dust.

Latency analysis for PVC dust (Fig. 1) shows a peak for the difference between observed minus expected dose during the period 5 to 16 years before death. As the diagnosis of the disease of interest becomes more narrowly defined as a pathologically homogeneous entity, the dose difference per case increases, yet the implied latent period stays constant.

Discussion

The first objective of this study was to determine if the excess lung cancer risk among employees exposed to VCM also existed for the total plant population, including those persons not exposed to VCM. The retrospective cohort mortality study showed that respiratory system cancers occurred approximately 50% more frequently among the employees of the entire plant than would have been expected based on age, sex, race, and calendar year specific United States death rates. A similar excess had been previously shown to exist among the subcohort of employees exposed to VCM (*1*). Thus, the excess lung cancer risk at the plant appeared to be independent of VCM exposure unless one hypothesized that it was due to extremely low levels of VCM that could have permeated throughout the plant.

Potentially confounding variables are age, sex, calendar year, race/ethnicity, migration, urban residence, cigarette smoking and socioeconomic status (SES). In the retrospective cohort study, age and calendar year cannot confound because they are adjusted in the results. All persons in the study are male and 98% are presumed white. White male specific rates were used for comparison to control those potential confounders by subject category restriction. Ethnicity and migration (both inter- and intracountry) effects are considered minimal for all three study designs because 42 of the 45 cases were born in Kentucky or an adjacent state. Urban residence is mainly associated with an excess of epidermoid and small cell undifferentiated lung cancer (*15*) rather than the histologic types of lung cancer found in excess in this study. Excess lung cancer risk is associated with low socioeconomic status (*16*, *17*), measured either by education (relative risk of 1.2 for persons with fewer than eight years of school) or by occupation (relative risk of 1.3 for laborers). Since the cohort consists of a mixture of socioeconomic status levels, there is probably insignificant confounding due to SES at the plant considered as a whole. Furthermore, recent infor-

Table 8. Probability value of paired *t*-tests of cumulative differences between observed and expected doses for lung cancer cases.

	Total (all years)[a]	10 or more years before death
All cases (N = 45)		
PVC dust	0.185	0.258
All pathologically reviewed cases (N = 27)		
PVC dust	0.026[b]	0.047[b]
Adenocarcinoma and large cell (N = 15)		
PVC dust	0.037[b]	0.061
Vinylidene chloride	0.267	0.333
Large cell (N = 8)		
PVC dust	0.068	0.177
Chlorinated solvents	0.360	0.435
Vinylidene chloride	0.201	0.322

[a]Twelve chemicals were tested for each lung cancer group, thus, under an assumption of independence of tests, one would expect one test to be significant at the 0.08 level.
[b]$p < 0.05$.

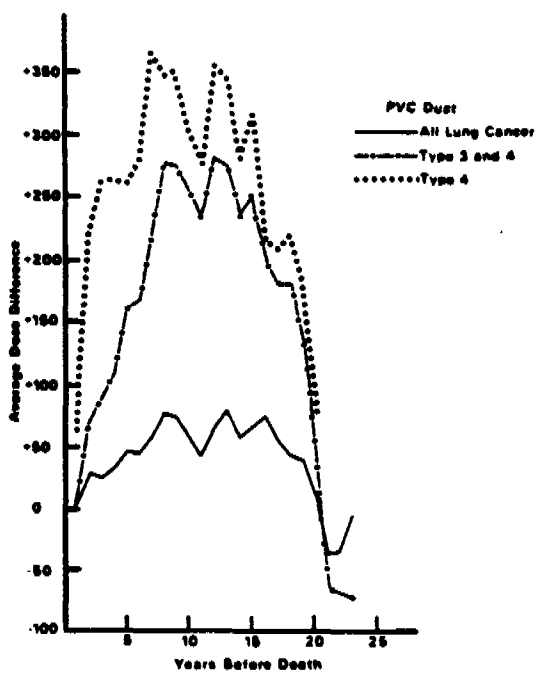

FIGURE 1. Observed minus expected dose differences per case among lung cancer cases for PVC dust.

mation indicates that these risk gradients may be partially due to smoking patterns (*18, 19*), which would affect epidermoid and small cell undifferentiated lung cancers.

The second objective of this research was to determine whether an excess lung cancer risk of a particular histologic type existed. The case-comparand study showed that there was an excess of adenocarcinomas and large cell undifferentiated lung cancers among the cases occurring among plant employees compared to other lung cancer cases from the same community. Because the pathologists reviewed both sets of slides without knowing which were those of plant employees, it is unlikely diagnostic biases occurred.

Histologic specimens were more difficult to find among the cases which died earlier and which were older on the date of death. However, community comparands were matched with the cases on age and date of diagnosis and had to have specimens available themselves; hence a biased ascertainment by histology between cases and comparands would be unlikely. The choice of community comparands makes it unlikely that a community wide pollutant was responsible for the excess risk at the plant for types 3 and 4 lung cancer. Consequently, it can be inferred from Table 3 that the excess lung cancer risk in the cohort was limited to adenocarcinoma and large cell undifferentiated cancer. Adenocarcinomas, accounting for a minor proportion of this excess risk, have been shown to be weakly, if at all, related to cigarette smoking (*14, 20-22*)

Large cell undifferentiated carcinoma of the lung is the only major histologic type that has appeared to be unrelated to cigarette smoking. Thus, cigarette smoking was probably not a major confounding variable. However, the role of smoking as a promoter or cocarcinogen cannot be ruled out. Nevertheless, the conclusion of this phase of the investigation was that an excess risk occurred among plant employees for types 3 and 4 lung cancer, especially type 4.

The third objective was to test whether one or more particular chemicals used at the plant were responsible for either the excess risk of all lung cancer or of the types 3 and 4 or just type 4 lung cancer. The SAED model was specifically developed for this objective.

The major hypothesis was tested for each chemical in the SAED model by using the one-sided *t*-test of the observed minus expected cumulative doses over all years before death and ten or more years before death (Table 8). PVC dust was the only chemical that was statistically significant. These results suggest that an excess of types 3 and 4 lung cancer exists at this plant and is related to PVC dust exposure.

The suggestion of PVC dust being a lung carcinogen is biologically plausible. Almost all PVC particles produced by the emulsion system, one of the systems at this plant, are in the respirable range (*23*). These particles could settle in the lungs and conceivably by themselves cause lung cancer. In fact, one case of supposedly PVC dust-induced pneumoconiosis has been found in a worker (*24*), and pulmonary granulomas (*25, 26*) have been induced in animals exposed to PVC dust. In a large proportional mortality study of 4341 deaths that occurred among PVC fabricators, persons expected to be exposed to VCM and PVC dust demonstrated a slight (PMR = 117) excess lung cancer risk (*27*).

VCM gas is easily inhaled, and possibly would be in contact with tissue only a short time before being either exhaled or absorbed into the bloodstream. However, VCM becomes entrapped in the PVC dust and can be released slowly over time. Thus, PVC dust particles in the lung may slowly release VCM to small adjacent areas of the tissue, prolonging the contact time of that chemical to tissue. If this latter hypothesis is true, then it begs the question of why almost all of the liver angiosarcoma cases occurred among polymer reactor cleaners who received extremely high VCM doses while the lung cancer cases occurred frequently among the less heavily exposed workers. In fact, there was no relationship between VCM and lung cancer in this analysis; yet, one would expect the lung to be the major route of entry for VCM regardless of the cancer site.

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Review of Pulmonary Effects of Poly(vinyl Chloride) and Vinyl Chloride Exposure

by Ruth Lilis*

The contributions of several recent reports to the definition of pulmonary effects of PVC dust inhalation are reviewed. Granulomatous reaction, with inclusion of PVC particles in macrophages and histocytes, and associated interstitial pulmonary fibrosis have been found to lead to exertional dyspnoea, diffuse micronodular chest radiographic opacities and restrictive pulmonary dysfunction.

The effects of vinyl chloride (VC) monomer (gas) on proteins and the immunologic mechanisms triggered by the altered protein are possible mechanisms for the development in some cases of interstitial pulmonary fibrosis secondary to VC exposure.

Vinyl chloride, a confirmed carcinogen, has been associated with, among other malignant tumors, a significant increase in the incidence of lung cancer. The magnitude of this effect has not yet been completely evaluated.

Several recent reports (*1-3*) have contributed new observations on pulmonary disease in vinyl chloride (VC)- and poly(vinyl chloride) (PVC)-exposed patients.

Earlier reports, a few even preceding the identification in 1974 of vinyl chloride as a human carcinogen (with hemangiosarcoma of the liver the marker tumor, but most probably not the only tumor), had centered on the rather unexpected occurrence of pulmonary radiologic abnormalities (*4-8*) or pulmonary function impairment (*4, 9-12*) or had indicated dyspnea as a prominent symptom (*11, 13*) in VC and/or PVC exposed workers.

The radiologic pattern first described in 1975 (*5*) was essentially that of reticular-linear and/or nodular (small rounded) opacities, involving both lungs, predominantly in the lower zones.

Pulmonary function abnormalities reported have been both restrictive and obstructive dysfunction with diffusion defects and arterial desaturation in some cases.

Three recent reports, one a case report (*1*), the other two epidemiologic surveys (*2, 3*), seem to identify PVC dust as the etiologic agent in a peculiar type of pulmonary fibrosis associated with a granulomatous reaction.

Exertional dyspnea, diffuse micronodular chest radiographic abnormalities and restrictive pulmonary dysfunction, were the main characteristics in the case of PVC pulmonary fibrosis associated with granulomatous lesions (*1*).

Electron microscopic examination of lung tissue showed giant multinucleated cells containing a nonhomogeneous material in their cytoplasm, which was identified to be PVC (*1*). A similar pattern was reproduced by incubation of human macrophages obtained by bronchial lavage, with PVC powder: absorption of PVC particles in the cytoplasm was rapid, with thinly granular lysosomal material deposited against the PVC particles.

Similar histologic lesions had been previously described in a human case (*4*) and in an experimental study in guinea pigs and rats (*14*). In another experimental study, intratracheal administration of PVC dust in rats (*15*) has been shown to result in an increase in the activity of lysosomal enzymes, interstitial fibrosis and granulomatous lesions surrounded by fibroblasts, reticulin and collagen fibers.

An epidemiologic study of a large group of workers exposed to PVC and VC (*2*) detected 20 cases of "typical pneumoconiosis," i.e., chest x-ray changes consisting in irregular opacities or micronodular shadows of at least class 1 profusion,

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according to the ILO U/C Classification. All these cases were found among PVC exposed employees. The pattern of radiologic abnormalities described is very similar to that reported in the case in which the lung biopsy revealed fibrosis and granulomatous reaction, with inclusion of PVC particles.

The same study reported the presence of less marked radiologic abnormalities, of the linear-reticular type, in a much larger proportion (32%) of the population examined; these changes were present both in VC monomer exposed and in PVC exposed employees. While the prevalence was higher in smokers than nonsmokers, 65 of the 388 x-rays with linear-reticular opacities were found in persons who had never smoked.

In another large epidemiologic study (*3*), exposure to respirable PVC dust was found to be associated in a proportion of exposed workers with the presence of small rounded opacities on the chest radiograph and a decline in mean ventilatory capacity.

The question of pulmonary effects due to vinyl chloride monomer continues to be of great interest. The multi-organ effects of vinyl chloride include the peculiar syndrome of acroosteolysis, scleroderma-like skin changes, vascular changes affecting the arteries, arterioles and capillaries of hands and fingers, liver and spleen capsular fibrosis, liver fibrosis, abnormalities of the sinusoidal vessels in the liver, and portal hypertension. Ward (*16*) investigated the immunologic status of 58 workers from a VC polymerization plant. The findings included hyperimmunoglobulinemia, cryoglobulinemia, cryofibrinogenemia, *in vivo* complement activation via the classic pathway, with C_4 and C_3 conversion and an increase in the B cell lymphocyte population. Immunofluorescent examination of skin, muscle and lung biopsy specimens revealed the presence of circulating immune complexes, with deposition on the vascular endothelium and occlusion of small vessels. Immunoglobulin, complement and fibrinogen deposition in the subintimal regions of the vessel were found in areas with subintimal fibrosis and luminal occlusion.

Grainger et al. (*17*) have accumulated evidence suggesting the following mechanism: the vinyl chloride metabolite cyclic chlorethylene epoxide, an alkylating agent with high biological activity binds to IgG producing structural conformational changes that promote aggregation of IgG molecules. The modified IgG may also become antigenic. The IgG aggregates are cryoprecipitable and may initiate complement activation. Precipitation of IgG aggregates by cold leads to complement activation, platelet aggregation and conversion of fibrinogen to fibrin with polymerization. Occlusion of small vessels results, and ischemia stimulates new collagen biosynthesis.

Similar abnormalities of the immunologic status were found in another study of 22 workers exposed to vinyl chloride, with Raynaud's syndrome and, in some cases, acroosteolysis. Latent cryoglobulinemia was detected in 18 cases, with increases of immunoglobulins, IgA and IgG (*18*).

Circulating cryoimmunoglobulins are a prominent feature of idiopathic pulmonary fibrosis (*19*) and increased IgG levels have been shown to be characteristic for bronchoalveolar lavage fluid of such patients.

Interstitial pulmonary fibrosis is a possible effect of vinyl chloride exposure. The occurrence of more dramatic and specific abnormalities in other organ systems—liver, spleen and peripheral circulation—has probably prevented more focused attention on pulmonary effects of vinyl chloride in the past.

Long-term effects of vinyl chloride include well documented carcinogenicity. Lung cancer has been found to occur with an increased incidence in several mortality studies (*20-22*). Abnormalities in sputum cytology tests have been found to be more frequent in VC/PVC-exposed workers than in other chemical industry employees and in smokers (*23*). In experiments on mice, Suzuki (*24*) has described hyperplastic changes of the alveolar lining cells and pulmonary tumors in the majority of exposed animals. The ultrastructure was thought to indicate that the tumors originated in type II alveolar cells. Alveologenic tumors were also described in several other experimental studies (*25-27*). Interestingly, other known carcinogens, such as polycyclic aromatic hydrocarbons, nitrogen mustard and chromates, produce pulmonary tumors in experimental animals similarly, originating in the type II alveolar cell.

The effects of vinyl chloride-poly(vinyl chloride) exposure on the respiratory system of exposed workers seem to indicate two patterns of nonmalignant effects: a granulomatous reaction to PVC dust, with inclusion of PVC particles in macrophages and histocytes and associated interstitial fibrosis, and an interstitial pulmonary fibrosis due to vinyl chloride monomer effects on protein molecules and the immunologic mechanisms triggered by the altered protein.

The long-term carcinogenic effect, with a significant increase in the incidence of lung cancer, also is of concern, although the magnitude of this effect has not yet been completely evaluated.

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1970 through 1978. The annual incidence rate for this period was also 0.25, almost double the expected rate of 0.14 per million in the United States (*8*). There are several possible explanations for these observations. New York is more industrialized than many other states, and it is possible that the exposed cohort might be larger. Increased recognition and reporting of this entity might also be a factor. Finally, relatively few workers have been exposed for a long time to high levels of vinyl chloride monomer.

As Fox and Collier (*17*) point out, more than half of the people who have ever been exposed to VCM in the manufacture of PVC in Great Britain are currently employed in the industry; approximately 75% of men who have been employed in the industry have been employed for less than 10 years; only 8% have been employed for 20 years or longer; approximately half the persons who have been exposed to VCM have been intermittently exposed; and only 10% of those who have been constantly exposed have been exposed to high concentrations. Thus it is possible that we are only beginning to see the full impact of industrial exposure to VCM. This suggestion is supported by the observation of Monson et al. (*18*) that the relative frequency of all cancers appears to be increasing with time in vinyl chloride workers.

Other factors must also be considered in examining the frequency of ASL in our society. Working conditions in the manufacture of PVC have undoubtedly been influenced since the early 1940s. This was largely due to the recognition after 1957 that exposure to high concentrations of VCM can cause acro-osteolysis (*19*) and Raynaud-like phenomena, and in the early 1970s that high concentrations of this chemical increase the risk of dying from ASL (*6*). A reasonable assumption is that earlier workers were probably exposed to higher concentrations of VCM than those who entered this industry during the last decade. Interestingly, it has recently been suggested that the age at diagnosis and latency period for ASL might be increasing (*15*). If verified, these preliminary observations

Table 1. Angiosarcoma of the liver (ASL) in residents of New York State (excluding New York City), 1970–1978.

Case	Age	Race[a]	Sex	Year of ASL diagnosis	Exposure history[b]	Metastatic site	Other tumors		
							Type	Site	Year of diagnosis
1	60	W	M	1970	Direct, VC	Adrenal, omentum	—		
2	45	W	F	1970	Possible, VC	Kidney, scalp, dura	—		
3	45	W	M	1970	—	Bone, adrenal	—		
4	18	B	F	1970	—	Spleen, lymph nodes	—		
5	55	W	F	1971	—	Spleen, omentum, adrenals, lymph nodes	—		
6	68	W	M	1971	—	—	Lymphosarcoma	Ileum	1955
7	4/12	W	F	1971	—	Lungs, adrenals, skin	—		
8	31	O	F	1972	Possible, VC	Heart, brain, lungs, adrenals	—		
9	77	W	M	1972	—	Spleen, marrow, lymph nodes	—		
10	64	W	F	1973	Direct, AS	—	Fibromyxolipo-sarcoma	Knee	1969
							Mesenchymoma	Liver	1973
11	47	W	M	1973	Direct, ThO_2	Brain, lymph nodes	—		
12	62	W	F	1973	Possible, VC	Spleen	—		
13	68	W	M	1973	—	Spleen, pancreas, adrenals, brain, bone, lungs, lymph nodes	Transitional cell carcinoma	Bladder	1973
14	59	W	M	1973	—	—	—		
15	31	W	F	1974	Possible, VC	—	—		
16	45	W	M	1974	—	—	—		
17	62	W	F	1974	—	—	—		
18	65	W	M	1975	Direct, VC	—	—		
19	73	W	M	1975	—	—	—		
20	43	W	M	1977	—	Spleen, brain, lungs, duodenum	—		
21	54	W	F	1977	—	—	—		
22	63	W	M	1977	—	—	—		
23	33	W	F	1978	—	—	—		
24	46	W	M	1978	—	—	—		

[a]W = White; B = black, O = oriental.
[b]VC = vinyl chloride, PVC = poly(vinyl chloride), As = arsenic, ThO_2 = thorium dioxide; possible = lived within one mile of VC or PVC factory.

ought be of great importance in evaluating the possibility that lower doses of VCM might be associated with ASL after a prolonged latency period.

Apart from the risk of ASL associated with industrial exposure to VCM, the possibility exists that nonoccupational exposure might also be associated with ASL. Block (*20*) has suggested that this disorder might result from chronic low level exposure to this chemical. Landrigan and Heath (*21*) found cases of ASL among workers at two poly(vinyl chloride) fabrication plants and in residents living nearby. A study in New York State (*16*) found that five individuals with ASL (but no apparent occupational exposure to VCM) lived in closer proximity to polymerization and fabrication plants than their matched controls. In a study of 10 patients with ASL in Wisconsin (*22*), one patient lived near a chemical company that made plastics and resins. These observations might be fortuitous and must be tempered by the preliminary evidence suggesting that no excess of ASL is found among PVC fabricators (*11*). At present there is no conclusive evidence associating this tumor with nonoccupational exposure to VCM. However, this issue and a closely related one—that chronic low dose exposure might be associated with an increased risk of ASL—require further evaluation. To fully appreciate the potential magnitude of this issue, one must consider both residential proximity to plants and other potential sources of public exposure. Estimates have been made that 4.6 million people live within five miles of United States monomer and polymer production facilities (*23*). During the years of uncontrolled emissions, it was calculated that the average exposure level to this population was approximately 17 PPB (*23*). Household use of aerosol products in enclosed spaces, even in short 30-sec bursts, could result in air concentrations of VCM as high as 400 ppm which can persist several hours after spraying (*9*, *10*).

The Biologic Spectrum of Vinyl Chloride

Reference has already been made to the association between VCM and acro-osteolysis, Raynaud-like disorders and ASL. It is also clear that this agent can induce nonmalignant liver disease. In Russia a form of chronic hepatitis was found in approximately 25% of VCM workers (*24*). In addition, Thomas et al. (*25*) documented the occurrence of portal hypertension associated with hepatic fibrosis (Banti's syndrome) in a study of the hepatic tissues obtained from 20 workers with industrial exposure.

Of great concern is the growing evidence suggesting that the spectrum of disorders associated with VCM might include certain other neoplastic diseases, pneumoconiosis and possibly excess fetal loss. Several mortality studies have been conducted in recent years. Monson et al. (*18*) found an apparent excess of lung and brain cancers. A slight excess of digestive tract, lymphatic and hematopoietic tumors was also observed. A historical prospective mortality study of 8384 men who had at least one year of occupational exposure to vinyl chloride demonstrated that cancers of the digestive system (primarily ASL), respiratory system and brain and lymphomas occurred more often than expected in those members with the greatest estimated exposure (*26*). Similar results were observed by Waxweiler et al. (*27*) in a retrospective cohort study of workers from four plants engaged in the polymerization of vinyl chloride for at least 15 years. Although observed numbers in each of these studies are quite small, the strength of these observations lie in their consistency. In addition inhalation studies by Viola et al. (*28*), Maltoni (*29*) and Neplinger et al. (*30*) have demonstrated that this chemical induces adenomas and adenocarcinomas of the lung, neuroblastoma of the brain, lymphoma and various other tumors in a variety of animal species. Two other studies are notable for the different results obtained. A mortality study of over 4000 deaths among current and former employees of 17 PVC fabricators from 1964 through 1973 found an excess of cancers of the breast and urinary organs among white females (*31*). Fox and Collier (*17*) studied 7000 men who were at some time between 1940 and 1974 exposed to VCM and found no evidence to support the hypothesis that cancers other than those of the liver are associated with this agent.

Vinyl chloride inhalation or PVC might cause abnormalities of pulmonary function and chest x-rays (*32*, *33*). Szende et al. (*34*) was the first to describe pneumoconiosis due to PVC. Although PVC dust appears to be the major offender, Lilis et al. (*32*) showed that inhalation of this agent induced less severe respiratory function abnormalities than simultaneous inhalation of VCM and PVC. In a more recent study of 1216 PVC production workers, 20 cases of pneumoconiosis were found. Duration of exposure was about 12 years, on the average, and never less than five years (*35*). This study also suggests that pulmonary changes are directly related to PVC dust, while VCM exposure alone fails to cause these changes (*35*).

Available evidence also suggests that VCM is mutagenic (*36*), and workers appear to have an excess of chromosomal aberrations in lymphocytes

when compared to nonexposed controls (*37*). Selikoff (*38*) found that fetal death rates among wives of VCM workers ranged from seven to 14 per 100 pregnancies. Infante et al. (*39*) conducted a case-control study of the pregnancy outcome among wives of workers exposed to VCM and found a significant excess of fetal loss in the exposed group. While suggestive, these observations require verification, particularly in view of the many factors known to influence pregnancy outcome.

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Review of Experimental Carcinogenesis by Compounds Related to Vinyl Chloride

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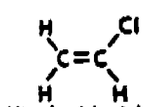
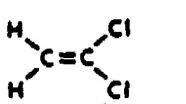
The experimental carcinogenesis results on six compounds related to vinyl chloride are reported. Vinylidene chloride, given by inhalation, was carcinogenic in male CD-1 mice, male CD rats, Sprague-Dawley rats and male Swiss mice. Trichloroethylene, given by gavage and inhalation, was carcinogenic in the B6C3F1 mice. When given by gavage, perchloroethylene was carcinogenic in the B6C3F1 mice, and dichloroethane was carcinogenic in Osborne-Mendel rats and B6C3F1 mice. Dibromoethane, given by gavage and inhalation, was carcinogenic in B6C3F1 mice, F344 rats and Osborne-Mendel rats. Finally, epichlorohydrin was carcinogenic in male Sprague-Dawley rats and B6C3F1 mice.

Introduction

Since the carcinogenicity of vinyl chloride (VC) was demonstrated in experimental (*1*) and epidemiologic studies (*2*), data on the potential carcinogenicity of vinyl chloride structural analogs and related compounds have been increasing. This paper will attempt to review the experimental carcinogenicity data on a number of these compounds, while another paper (*3*) will discuss the epidemiologic results.


Vinyl chloride
VC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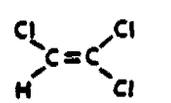
VDC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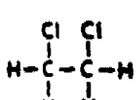
TCE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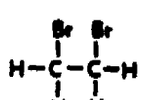
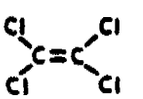
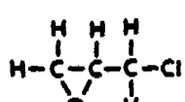
DCE


1,2-Dibromoethane
DBE


Tetrachloroethylene
PCE


Epichlorohydrin
EPC

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Results

Vinylidene Chloride (VDC)

A summary of some of the carcinogen bioassays of vinylidene chloride is given in Table 1. The strongest evidence of a carcinogenic effect was in a bioassay involving Swiss mice performed by Maltoni et al. (*4*, *5*). In this study, 24/150 dosed male mice had kidney tumors as compared to 0/190 in the controls. In the study by Lee et al. (*6*, *7*), dosed CD-1 mice and CD rats had two or three liver angiosarcomas. Since this type of tumor was induced by vinyl chloride in humans and rodents and the study was terminated after only one year, the results are viewed as biologically significant. In an inhalation study in Sprague-Dawley rats by Maltoni et al. (*4*, *5*), increases in mammary gland tumors in the dosed animals were reported. However, these incidences did not follow a dose-response relationship.

In contrast to these positive studies, a number of nonpositive two-year carcinogen bioassay studies have been reported (*6-9*). Most notable is this initial report that preliminary evaluations of vinylidene chloride in a two-year National Toxicology Program (NTP)/NCI bioassay of Fischer 344 rats, given at 2-10 mg/kg of body weight and of B6C3F1 mice, given at 1-5 mg/kg of body weight, did not indicate any significant increased incidences of tumors in the dosed animals as compared to controls.

Trichloroethylene (TCE)

A summary of some of the carcinogen bioassays of trichloroethylene is reported in Table 2. In B6C3F1 mice, this compound, given by gavage, was found to be carcinogenic, inducing hepatocellular tumors (*10*). In confirmation of this finding, an inhalation study in B6C3F1 mice, performed by Biotest Laboratories, gave similar results (*11*).

Bioassays of TCE were nonpositive in two strains of rats, the Sprague-Dawley and Osborne-Mendel (*10-12*). Additional NTP/NCI carcinogen bioassays are under way in five strains of rat and the B6C3F1 mice to examine species and strain differences.

Tetrachloroethylene (Perchloroethylene) PCE

The carcinogen bioassay results of testing PCE are given in Table 3. In B6C3F1 mice, this compound, given by gavage, was carcinogenic inducing hepatocellular tumors.

Studies in two strains of rats, Osborne-Mendel and Sprague-Dawley, produced no carcinogenic effects (*13-14*). Additional carcinogen bioassays in four strains of rats and the female B6C3F1 mice are currently underway at NTP/NCI.

1,2-Dichloroethane (DCE)

The experimental carcinogenicity results of testing DCE are given in Table 4. In B6C3F1 mice, the

Table 1. Bioassays of vinylidene choride (VDC).

Species/Str[a]	Route (vehicle)[b]	Sex	Dose ppm or mg/kg[c]	Dosing period (duration), wk	Group size	Target site (tumor incidences)[d]	Reference
Mouse, CD-1	Inhal	M	55	52D(52)	36	Liver, hemangiosarcoma	(6,7)
			0	"	36	(2/35 0/26)	
		F	55	52D(52)	36	Liver, hemangiosarcoma	
			0	"	36	(1/35 0/36)	
Rat, CD	Inhal	M	55	52D(52)	36	Hemangiosarcoma	(6,7)
			0	"	36	(2/36 0/35)	
		F	55	52D(52)	36	NSC	
			0	"	36		
Rat, Spr-Daw	Inhal	M	150	52D(life)	60	NSC	(4,5)
			100	" "	30		
			50	" "	30		
			25	" "	30		
			10	" "	30		
			0	" "	100		
		F	150	52D(life)	60	Mammary gland	
			100	" "	30	(nondose response)	
			50	" "	30		
			25	" "	30		
			10	" "	30		
			0	" "	100		

Table 1 (cont.)

Species Str[a]	Route (vehicle)[b]	Sex	Dose ppm or mg/kg[c]	Dosing period (duration), wk	Group size	Target site (tumor incidences)[d]	Reference
Mouse, Swiss	Inhal	M	25	52D(life)	150	Kidney	(4, 5)
			10	" "	30	(24/150 0/190)	
			0	" "	190		
		F	25	52D(life)	150	NSC	
			10	" "	30		
			0	" "	190		
Rat, Spr-Daw	Gav (Olive oil)	M	20	52D(life)	50	NSC	(4, 5)
			10	" "	50		
			5	" "	50		
			0	" "	50		
		F	20	52D(life)	50	NSC	
			10	" "	50		
			5	" "	50		
			0	" "	50		
Hamster, Chin	Inhal	M	25	52D(life)	30	NSC	(4, 5)
			0	" "	30		
		F	25	52D(life)	30	NSC	
			0	" "	30		
Mouse B6C3F1 (NCI)	Gav (Corn oil)	M	10	(103)	50	NSC*	
			2	"	50		
					50		
		F	10	(103)	50	NSC*	
			2	"	50		
			0	"	50		
Rats, F344 (NCI)	Gav (Corn oil)	M	5	(103)	50	NSC*	
			1	"	50		
			0	"	50		
		F	5	(103)	50	NSC*	
			1	"	50		
			0	"	50		
Rat, Spr-Daw	Inhal	M	75	78D(104)	86	NSC	(8)
			25	"	85		
			0	"	86		
		F	75	78D(104)	86	NSC	
			25	"	84		
			0	"	88		
Rat, Spr-Daw	Water	M	200	(104)	47	NSC	(8)
			100	"	48		
			60	"	48		
			0	"	80		
		F	200	(104)	47	NSC	
			100	"	48		
			60	"	48		
			0	"	80		
Rat, Wistar	Inhal	M	200–100	52D(104)	51	NSC	(9)
			0	"	30		
		F	200–100	52D(104)	28	NSC	
			0	"	30		
Rat, Spr-Daw	Inhal	M	100	52D(104)	30	NSC	(9)
			75	" "	16		
			0	" "	30		
		F	100	52D(104)	30	NSC	
			75	" "	21		
			0	" "	30		

[a]Chin = Chinese hamster; F344 = Fischer 344 rat; Spr-Daw = Sprague-Dawley rat.
[b]Gav = gavage; Inhal = inhalation.
[c]Units: ppm for inhalation; mg/kg for other routes.
[d]NSC = Not shown to be carcinogenic.
*Preliminary results.

compound, given by gavage, was carcinogenic, inducing lung tumors in both sexes and mammary gland and uterus tumors in dosed female animals (*15*). The chemical was also carcinogenic in Osborne-Mendel rats, giving forestomach tumors and extrahepatic hemangiosarcomas in both sexes, subcutaneous fibromas in the males and mammary gland tumors in the females (*15*).

In contrast, a preliminary report by Maltoni (*12*) indicated that DCE was not shown to be carcinogenic in an inhalation study with Swiss mice and Sprague-Dawley rats. Since there were strain and

Table 2. Bioassays of trichloroethylene (TCE).

Species/Str[a]	Route (vehicle)[b]	Sex	Dose, mg/kg	Dosing period (duration), wk	Group size	Target site (tumor incidences)[c]	Reference
Mouse B6C3F1[d]	Gav (Corn oil)	M	2339	78D(90)	50	Liver, hepatocellular (31/48 26/50 1/20)	(*10*)
			1169	" "	50		
			0	" "	20		
		F	1739	78D(90)	50	Liver, hepatocellular 11/47 4/50 0/20)	
			869	" "	50		
			0	" "	20		
Mouse B6C3F1[d]	Inhal	M	600 ppm	(104)	100	Liver, hepatocellular (43/97 31/100 28/95 18 99)	(*11*)
			300 ppm	"	100		
			100 ppm	"	100		
			0	"	100		
		F	600 ppm	(104)	100	Liver, hepatocellular (13/99 9/94 4/100 6/99)	
			300 ppm	"	100		
			100 ppm	"	100		
			0	"	100		
Rat, Osb-Mdl[d]	Gav (Corn oil)	M	1097	78D(110)	50	NSC	(*10*)
			549	" "	50		
			0	" "	20		
		F	1097	78D(110)	50	NSC	
			549	" "	50		
			0	" "	20		
Rat, Spr-Daw	Gav (Olive oil)	M	250	52D(140)	30	NSC	(*12*)
			50	" "	30		
			0	" "	30		
		F	250	52D(140)	30	NSC	
			50	" "	30		
			0	" "	30		
Rat, Charles River[d]	Inhal	M	600 ppm	(104)	100	NSC	(*11*)
			300 ppm	"	100		
			100 ppm	"	100		
			0	"	100		
		F	600 ppm	(104)	100	NSC	
			300 ppm	"	100		
			100 ppm	"	100		
			0	"	100		
Rat, Marshall (NCI)	Gav (Corn oil)	M	1000	(110)	50	Assay still in progress	
			500	"	50	St. 2/79	
			0	"	50		
		F	1000	(110)	50	Assay still in progress	
			500	"	50		
			0	"	50		
Rat, ACI (NCI)	Gav (Corn oil)	M	1000	(110)	50	Assay still in progress	
			500	"	50	St. 2/79	
			0	"	50		
		F	1000	(110)	50	Assay still in progress	
			500	"	50		
			0	"	50		
Rat, F344 (NCI)	Gav (Corn oil)	M	1000	(110)	50	Assay still in progress	
			500	"	50	St. 6/78	
			0	"	50		
		F	1000	(110)	50	Assay still in progress	
			500	"	50		
			0	"	50		

Table 2 (cont.)

Species/Str[a]	Route (vehicle)[b]	Sex	Dose, mg/kg	Dosing period (duration), wk	Group size	Target site (tumor incidences)[c]	Reference
Rat, Osb-Mdl NCI)	Gav (Corn oil)	M	1000	(110)	50	Assay still in progress	
			500	"	50	St. 12/79	
			0	"	50		
		F	1000	(110)	50	Assay still in progress	
			500	"	50		
			0	"	50		
Rat, August NCI)	Gav (Corn oil)	M	1000	(110)	50	Assay still in progress	
			500	"	50	St. 10/79	
			0	"	50		
		F	1000	(110)	50	Assay still in progress	
			500	"	50		
			0	"	50		
Rat, B6C3F1 NCI)	Gav (Corn oil)	M	1000	(110)	50	Assay still in progress	
			0	"	50	St. 6/78	
		F	1000	(110)	50	Assay still in progress	
			0	"	50		

[a]F344 = Fischer 344 rat; Osb-Mdl = Osborne-Mendel rat; Spr-Daw = Sprague-Dawley rat.
[b]Gav = gavage, Inhal = inhalation.
[c]NSC = Not shown to be carcinogenic.
[d]With 0.09% epichlorohydrin.

dose differences as well as route of administration differences between the NTP/NCI and Maltoni studies, the causes of the differences in the experimental results are not readily apparent.

1,2-Dibromoethane (DBE)

The results of some carcinogen bioassays on DBE are given in Table 5. In bioassays on B6C3F1 mice and Osborne-Mendel rats, DBE given by gavage was carcinogenic, inducing multiple tumors in each species and sex. There were not only chemically induced tumors at the site of application (forestomach tumors) but also tumors distant from the site of application (lung tumors in mice and extrahepatic hemangiosarcomas in male rats and hepatocellular tumors in female rats) (*16*).

In addition, a preliminary analysis of an inhalation study of DBE performed by NTP/NCI indicates that nasal cavity tumors were found in dosed rats and dosed female mice. Furthermore, elevated incidences of lung tumors were found in the dosed mice as well as elevated incidences of mammary gland tumors in dosed females of each test species. Mesotheliomas were also induced by DBE in male rats.

Epichlorohydrin (EPC)

The bioassay results on epichlorohydrin are given in Table 6. Recently, this compound, given by inhalation, was found to be carcinogenic inducing nasal cavity tumors in male rats (*17*). In addition, experiments by Van Duuren (*18-19*) indicated that EPC was an initiator in a two-stage study and induced local sarcomas by subcutaneous injection. addition more comprehensive epidemiological studies involving the manufacture, production and use of these compounds should be undertaken.

A summary of some of the bioassay results for each compound by species/strain is given in Table 7.

Discussion

The data on these compounds can generate some interesting points for discussions, such as the probable mechanism of some of these compounds, the controversy over TCE results and suggestions for future action.

In the first case, studying the summary table indicates that the compounds (DBE, DCE, and EPC) which are proposed to alkylate directly, gave forestomach tumors when given by gavage or nasal cavity tumors when given by inhalation while the compounds which are proposed to require metabolic activation did not produce these types of tumors. One can envision that these compounds, due to their alkylating ability and their ability to induce site of application tumors, are direct-acting carcinogens. Two of these former compounds, DBE and

Table 3. Bioassays of perchloroethylene (PCE).

Species/Str[a]	Route (vehicle)[b]	Sex	Dose, mg/kg	Dosing period (duration), wk	Group size	Target site (tumor incidences)[c]	Reference
Mouse B6C3F1	Gav (Corn oil)	M	1072	78D(90)	50	Liver, hepatocellular (27/48 32/49 2/20)	(13)
			536	" "	50		
			0	" "	20		
		F	772	78D(90)	50	Liver, hepatocellular (19/48 19/48 0/20)	
			386	" "	50		
			0	" "	20		
Rat, Osb-Mdl	Gav (Corn oil)	M	941	71D(110)	50	NSC	(13)
			471	" "	50		
			0	" "	20		
		F	949	71D(110)	50	NSC	
			474	" "	50		
			0	" "	20		
Rat, Spr-Daw	Inhal (Corn oil)	M	600 ppm	52D(135)	96	NSC	(14)
			300 ppm	" "	96		
			0	" "	96		
		F	600 ppm	52D(135)	96	NSC	
			300 ppm	" "	96		
			0	" "	96		
Rat, Sherman (NCI)	Gav (Corn oil)	M	750	(103)	50	Assay still in progress St. 2/78	
			375	"	50		
			0	"	50		
		F	750	(103)	50	Assay still in progress	
			375	"	50		
			0	"	50		
Rat, Wistar (NCI)	Gav (Corn oil)	M	750	(103)	50	Assay still in progress St. 11/78	
			375	"	50		
			0	"	50		
		F	750	(103)	50	Assay still in progress	
			375	"	50		
			0	"	50		
Rat, Long-Evans (NCI)	Gav (Corn oil)	M	750	(103)	50	Assay still in progress St. 7/78	
			375	"	50		
			0	"	50		
		F	750	(103)	50	Assay still in progress	
			375	"	50		
			0	"	50		
Rat, F344 (NCI)	Gav (Corn oil)	M	750	(103)	50	Assay still in progress St. 9/78	
			375	"	50		
			0	"	50		
		F	750	(103)	50	Assay still in progress	
			375	"	50		
			0	"	50		
Rat, B6C3F1 (NCI)	Gav (Corn oil)	F	200	(103)	100	Assay still in progress	
			100	"	100		
			50	"	100		
			25	"	100		
			0	"	100		

[a]F344 = Fischer 344 rat; Osb-Mdl = Osborne-Mendel rat; Spr-Daw = Sprague-Dawley rat.
[b]Gav = gavage; Inhal = inhalation.
[c]NSC = Not shown to be carcinogenic.

DCE, also induced tumors distant from the site of application. This fact may be an important point in the controversy over TCE.

This controversy stems from the fact that the results on TCE indicated that the mice studies were positive while the rat studies showed the chemical did not produce a carcinogenic effect. There have been several explanations. It has been postulated that epichlorohydrin, used as a stabilizer in the TCE tested, is responsible for the positive effect, not TCE (21). The NCI Technical report on TCE (10) indicated that there was 0.09% EPC in

Table 4. Bioassays of 1,2-dichloroethane (DCE).

Species/Str[a]	Route (vehicle)[b]	Sex	Dose, mg/kg	Dosing period (duration), wk	Group size	Target site (tumor incidences)[c]	Reference
Mouse, B6C3F1	Gav (Corn oil)	M	195	78D(91)	50	Lung	(15)
			97	" "	50	(15/48 1/47 0/19)	
			0		20		
		F	299	78D(91)	50	Lung (15/48 7/50 1/20)	
			149	" "	50	Mammary gland (7/48 9/50 0/20)	
			0		20	Uterus (5/47 5/49 0/20)	
Rat, Osb-Mdl	Gav (Corn oil)	M	95	69D(110)	50	Forestomach (9/50 3/50 0/10)	(15)
			47	" "	50	Hemangiosarcoma (7/50 9/50 0/20)	
			0		20	SQ Fibroma (6/50 5/50 0/20)	
		F	95	69D(93)	50	Mammary gland	
			47	(110)	50	(18/50 1/50 0/20)	
			0		20		
Mouse, Swiss	Inhal	M	250–150 ppm	(life)	90	NSC[d]	(12)
			50 ppm	"	90		
			10 ppm	"	90		
			5 ppm	"	90		
			0	"	180		
		F	250–150 ppm	(life)	90	NSC[d]	
			50 ppm	"	90		
			10 ppm	"	90		
			5 ppm	"	90		
			0	"	180		
Rat, Spr-Daw	Inhal	M	250–150 ppm	(life)	90	NSC[d]	(12)
			50 ppm	"	90		
			10 ppm	"	90		
			5 ppm	"	90		
			0	"	90/180		
		F	250–150 ppm	(life)	90	NSC[d]	
			50 ppm	"	90		
			10 ppm	"	90		
			5 ppm	"	90		
			0	"	90/180		

[a]Osb-Mdl = Osborne-Mendel rat; Spr-Daw = Sprague-Dawley rat.
[b]Gav = gavage; Inhal = inhalation.
[c]NSC = Not shown to be carcinogenic.
[d]Preliminary results.

the TCE. The doses of TCE were about 2000-1000 mg/kg of body weight, corresponding to less than 2 mg/kg of body weight of epichlorohydrin. If epichlorohydrin is the active agent, one might expect forestomach tumors from a gavage study because of its alkylating ability. However, the target site in the mice is the liver. In addition, if epichlorohydrin is the carcinogen, then why are the results negative in the rat? Direct-acting carcinogens, like epichlorohydrin, are less likely to show such a species difference than compounds which would require metabolic activation, such as TCE itself. Thus, an alternative explanation is that there is a species difference reflecting some type of metabolic or target site sensitivity difference between the species.

The answer may be forthcoming. NTP/NCI is testing TCE without EPC in the B6C3F1 mice and five strains of rat. If EPC is the active compound, the mice study should not show a carcinogenic effect. However, if TCE is the active agent then the B6C3F1 mouse study should be positive. The results in the rats will also give insight into whether there is a species or a species/strain difference for TCE. Similar types of studies are also underway with PCE. In addition, Maltoni has indicated that he has started bioassays on TCE with B6C3F1 mice and Swiss mice.

With the possible resolution of the TCE issue, there still remains the differences in experimental results involving vinylidine chloride (VDC). The results in VDC may indicate that there are important species and strain differences. As a consequence, this compound may be an ideal candidate for studying species/strain differences systematical-

Table 5. Bioassays of 1,2-dibromethane (DBE).

Species/Str[a]	Route (vehicle)[b]	Sex	Dose, mg/kg	Dosing period (duration), wk	Group size	Target site (tumor incidences)	Reference
Mouse B6C3F1	Gav (Corn oil)	M	107	53D(78)	50	Forestomach (29/49 45/50 0/20)	(16)
			62	" "	50	Lung (10/47 4/45 0/20)	
			0	"	20		
		F	107	53D(90)	50	Forestomach (28/50 46/49 0/20)	
			62	" "	50	Lung (6/46 11/48 0/20)	
			0	(60)	20		
Rat, Osb-Mdl	Gav (Corn oil)	M	41	34D(49)	50	Forestomach (33/50 45/50 0/20)	(16)
			88	47D"	50	Hemangiosarcoma	
			0	(63)	20	(4/50 11/50 0/20)	
		F	39	44D(61)	50	Forestomach (29/50 40/50 0/20)	
			87	57D"	50	Liver, hepatocellular	
			0	(63)	20	(5/48 1/47 0/20)	
Mouse B6C3F1 (NCI)	Inhal	M	40 ppm	(103)	50	Lung (19/46 3/48 0/41)[c]	
			10 ppm	"	50		
			0	"	50		
		F	40 ppm	(103)	50	Nasal cavity (6/50 0/50 0/50)[c]	
			10 ppm	"	50	Mammary gland (8/50 14/50 2/50)[c]	
			0	"	50	Lung (37/50 5/49 1/49)[c]	
Rat, F344 (NCI)	Inhal	M	40 ppm	(103)	50	Nasal cavity (28/50 20/50 0/50)[c]	
			10 ppm	"	50	Mesothelioma	
			0	"	50	(25/50 7/50 1/50)[c]	
		F	40 ppm	(103)	50	Nasal cavity (29/50 20/50 0/50)[c]	
			10 ppm	"	50	Mammary gland	
			0	"	50	(24/50 29/50 4/50)[c]	

[a]F344 = Fischer 344 rat; Osb-Mdl = Osborne-Mendel rat.
[b]Gav = gavage; Inhal = inhalation.
[c]Preliminary results.

Table 6. Bioassays of epichlorohydrin (EPC).

Species/Str[a]	Route (vehicle)[b]	Sex	Dose	Dosing period (duration), wk	Group size	Target site (tumor incidences)[c]	Reference
Rat, Spr-Daw	Inhal	M	100 ppm	6D(life)	140	Nasal cavity	(17)
			30 ppm	(life)	100	(15/140 2/100 0/100 0/50)	
			0	"	100		
					50		
Mouse, ICR/Ha Swiss	SC	F	1 mg in 0.1 ml tricaprylin wkly	(life)	50	Local sarcomas (2/50 0/50)	(19)
Mouse, ICR/Ha Swiss	SC	F	1 mg in 0.05 ml tricaprylin wkly	(life)	50	Local sarcomas (7/50 1/50)	(18)
Mouse	Skin		1 mg in 0.1 ml acetone then 2.5 g phorbol myristate[c]	1 dose 55D	30	Initiator (10/30 3/30)	(18)
Mouse, C3H	Skin	—	1 Br	(life)	40	NSC	(20)
Mouse, ICR/Ha	Skin	F	2 mg in 0.1 ml acetone 3/wk	57D(57)	50	NSC	(18)
Mouse, ICR/Ha	IP	F	1 mg in 0.05 ml tricaprylin wkly	(64)	30	NSC	(18)

[a]Spr-Daw = Sprague-Dawley rat.
[b]IP = intraperitoneal injection; SC = subcutaneous injection; Skin = skin painting.
[c]NSC = Not shown to be carcinogenic.

Table 7. Summary of bioassay results on vinyl chloride analogs and related compounds for some tumor sites.

	VC	VDC	TCE	PCE	DCE	DBE	ECH
Hemangio-sarcoma	SD Rat-G Mouse-I[a] Rat-I[a]	m-CD-1 Mouse-I m-CD Rat-I			m-OM Rat-G	m-OM Rat-G	
Lung tumors	Mouse-I[a] Rat-I[a]				B6C3P1-G	B6C3F1-G B6C3F1-G[b]	
Mammary gland tumors (females)	Mouse-I[a]	SD Rat-I			OM Rat-G B6C3F1-G	F344 Rat-I[b] B6C3F-I[b]	
Kidney tumors		m-Sw Mouse-I					
Hepatocellular tumors			B6C3F1-G B6C3F1-I	B6C3F1-G		f-OM Rat-G	
Forestomach tumors					m-OM Rat-G	OM Rat-G B6C3F1-G	
Nasal cavity tumors						F344 Rat-I[b] f-B6C3F1-I[b]	m-SD Rat-I
Local sarcoma							f-ICR/Ha Sw Mouse-SP
NSC		F344 Rat-G[b] B6C3F1-G[b] Wis Rat-I Ch Harn-I SD Rat-W SD Rat-I SD Rat-G	OM Rat-G SD Rat-G CR Rat-I	OM Rat-G SD Rat-G	SD Rat-I Sw Mouse-I		

[a]Effect seen in at least two strains.
[b]Preliminary results on NTP/NCI studies.

ly. In addition, the differences in the NCI and Maltoni studies on DCE could be the source for additional research.

From an examination of Table 7, the compounds with positive results in multiple species yielding multiple tumor sites are the direct acting carcinogens, DBE and DCE. (EPC has not been tested extensively yet.) This strong evidence in experimental carcinogenesis should, at least, trigger measures to decrease exposure to these compounds. In addition more comprehensive epidemiological studies involving the *manufacture, production* and use of these compounds should be undertaken.

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Review of Epidemiologic Study Results of Vinyl Chloride-Related Compounds

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Epidemiologic study results addressing the carcinogenicity of six compounds related to vinyl chloride (vinylidene chloride, trichloroethylene, perchloroethylene, carbon tetrachloride, ethylene dibromide and epichlorohydrin) are reviewed.

The study results suggest an increased carcinogenic risk among workers exposed to epichlorohydrin and to dry cleaning and degreasing solvents. Although several studies report no significant excess of cancer mortality, an evaluation of the design of these investigations demonstrates that these negative cohort studies consisted of populations of insufficient sample size and latency to permit any meaningful conclusions regarding carcinogenic risk. Therefore, experimental studies must be relied upon to determine whether several of these substances pose a potential carcinogenic risk to humans. Available evidence indicates that all of these substances have demonstrated a carcinogenic response in experimental animals and most are mutagenic in experimental test systems.

Introduction

In the early 1970's, bioassays demonstrated the induction of cancer at multiple sites in experimental animals exposed to vinyl chloride (VC) by several routes of administration. Subsequently, epidemiologic studies confirmed an excess cancer risk of multiple sites among individuals employed in operations using VC (*1*). As a result of these observations, attention was focused on the toxicity of structural analogs of vinyl chloride. This review will present information on the potential for human exposure and the carcinogenic risks associated with exposure to these substances.

Magnitude of Exposure

Studies of occupational groups exposed to six VC-related substances have been conducted. Estimates of the annual production, number of worker exposures derived from 1972-74 National Occupational Hazard Survey data and current OSHA permissible exposure limits expressed as 8-hr time-weighted averages (TWA), for levels of occupational exposure to these substances are presented in Table 1. These substances are produced in high volume, and exposures involve large numbers of workers. As some of these substances were not produced in relatively high volume until the 1950's (*2*), the latency period required for the statistically sensitive evaluation of any potential cancer risk in the exposed individuals has not yet been achieved for a large proportion of exposed individuals.

Table 2 presents occupations and industrial uses for six substances structurally or industrially related to VC. Epichlorohydrin (ECH) is used in the manufacture of epoxy resins and has been used as a chemical stabilizer in trichloroethylene (TCE) and in plastics. Vinylidene chloride (VDC) is used in the manufacture of copolymers and fibers. Ethylene dibromide (EDB) is used in the manufacture of petroleum products and as a pesticide. TCE, perchloroethylene (PCE) and carbon tetrachloride (CCl_4) are used in metal degreasing operations. Although TCE and CCl_4 have been used as dry cleaning solvents in the past, PCE is the major dry cleaning solvent in use today.

Experimental evidence now demonstrates that many of the compounds structurally and industri-

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ally related to vinyl chloride are carcinogenic (3). Many of these substances are also mutagenic (4, 5). Bioassay study results have demonstrated the induction of tumors at multiple sites as a result of exposure to EDB and CCl_4. Cancers of the respiratory tract have been induced in experimental animals exposed to EDB and ECH. Liver cancers have been induced in animals exposed to VDC and EDB as well as to the industrial solvents TCE, PCE and CCl_4.

While these experimental studies were being conducted, the Interagency Regulatory Liaison Group (IRLG) was drafting documentation guidelines for epidemiologic studies (6). Also during this time, hearings on OSHA's cancer policy were proceeding, with much emphasis given to the role of nonpositive epidemiologic studies in qualitative risk assessment. The epidemiologic considerations, expressed in the IRLG guidelines and discussed in the OSHA cancer policy (7) will be used in this paper to assess the methodology and results of several epidemiologic studies of populations potentially exposed to one or more of the structural analogs of vinyl chloride.

Epidemiologic Study Results

A study of workers exposed to ECH was reported by Enterline in 1978 (8). These data were analyzed by using the NIOSH life table program (9) and are presented in the summary data table (Table 3). Members of the cohort were employed for more than one quarter of a year any time between 1948 to 1966, and followed through the end of 1977. Expected numbers of deaths were based on U.S. age, sex, race and calendar time-period specific rates. Ninety-four percent of the employees had achieved a minimum of 15 years of latency. Fifty-one deaths from all causes were observed, and 82 were expected. Thirteen deaths due to cancer were observed compared to 14.2 expected. Though not statistically significant, a doubling of the lung cancer risk was observed among individuals who had achieved a latency period of at least 15 years since first exposure to ECH. For the entire cohort, eight lung cancers were observed when 4.9 were expected. These data suggest that workers exposed to ECH may be at an increased risk of lung cancer, but further follow-up is necessary to in order to achieve

Table 1. Estimates of U.S. annual production, number of worker exposures, and OSHA time-weighted averages for VC and structural analogs.

Carcinogenic substance	Annual U.S. production, lb × 10^8	Estimated number of worker exposures	OSHA TWA, ppm[b]
Epichlorohydrin (ECH)	220[c]	85,000	5
Vinylidene chloride (VDC)	200[d]	6,500–58,000	None
Trichloroethylene (TCE)	300[c]	282,000	100
Perchloroethylene (PCE)	770[e]	500,000	100
Carbon tetrachloride (CCl_4)	704[e]	160,000–2,000,000	10
Ethylene dibromide (EDB)	230[c]	9,000–660,000	20
Vinyl chloride (VC)	7544[e]	27,000–2,200,000	1

[a]International Trade Commission estimates.
[b]TWA = 8-hr time-weighted average.
[c]1978 estimates.
[d]Year not available.
[e]1979 etimates.

Table 2. Industrial uses and potential occupations with exposure to six carcinogenic substances.

Substance[a]	Major uses	Major occupational exposure industries
ECH	Manufacture of epoxy resins, surface active agents, and other chemicals	Assemblers, machinists, painters, chemical workers
VDC	Manufacture of copolymers and modacrylic fibers	Chemical workers, plastics workers
TCE	Metal degreasing, organic solvent	Chemical workers, metal workers, textile processing
PCE	Dry cleaning and textiles, metal cleaning, chemical manufacturing	Dry cleaners, chemical workers, textile workers, metal workers
CCl_4	Chemical manufacturing, grain fumigation, organic solvent	Chemical workers, grain fumigators
EDB	Fumigant, fuel additive, organic solvent	Chemical workers, petroleum products, exterminators and fumigators

[a]See Table 1.

a more sensitive estimate of the carcinogenic risk in humans. Several factors should be considered in evaluating these data. Some cohort members had been employed in the manufacture of isopropyl alcohol (IPA). This process has been associated with nasal sinus cancer, but the data to date have not demonstrated an excess of lung cancer among workers employed in the manufacture of IPA. In addition, the size of the cohort was small, and the average age of the cohort members during the followup period was only 48 years. The young age of the cohort is reflected in the low SMR of 63 for the entire cohort. Nevertheless, the data appear to be consistent with results of experimental bioassay which demonstrate ECH-induced cancers of the respiratory system.

Shellenberger et al. (*10*) reported on the mortality experience of 553 white male employees potentially exposed to ECH for at least one month between October 1957 and November 1976. Expected numbers of deaths were based on death rates for the Texas white male population for 1960 and 1970. Cause-specific observed and expected deaths and standardized mortality ratios for the entire cohort and for a subcohort employed in at least one job with a TWA of greater than 1 ppm were calculated. Twelve deaths were observed among cohort members, compared to 20.7 expected. No specific cause of death was in excess. Only two cancer deaths were observed compared to 3.5 expected. This cohort has not been observed for a long enough time period, as only 13% of the cohort had a latency of 15 or more years since employment.

Ott et al. (*11*) reported on the mortality experience of 138 employees exposed to VDC at any time between 1942 and 1968 and followed through 1973. Mortality among the exposed group was compared to the expected based on U.S. white male mortality rates. Five deaths were observed, compared to 7.5 expected. Only one cancer death was observed, compared to 1.1 expected. Clearly, the sample size is too small to allow any meaningful conclusion.

Axelson et al. (*12*) reported on the mortality experience of 518 male workers exposed to TCE in the 1950's and 1960's and followed through 1975. Eleven deaths from cancer occurred in the total cohort when 14.5 were expected. Among the subcohort who had achieved at least 10 years since first exposure, 9 deaths from all cancers were observed compared to 9.5 expected. The number of deaths from tumors are too small to analyze by site specific risk.

Table 3. Observed and expected deaths from studies of workers exposed to selected halogenated hydrocarbons.

Substance	Study	Total deaths			Total cancer deaths			Site-specific cancer deaths			
		Obs.	Exp.	SMR	Obs.	Exp.	SMR	Site	Obs.	Exp.	SMR
ECH	Enterline (*8*) Brown and Rinsky (*9*)	51	81.7	63	13	14.2	92	Respiratory	8	5.2	154
								Lung	8	4.9	163
								Digestive	2	3.4	58
								Lymphatic	2	1.9	103
	Subcohort ≥ 15 yr latency	33	44.6	74	12	8.9	135	Lung	7	3.5	200
ECH	Shellenberger (*10*)	12	20.7	58	2	3.5	57				
VDC	Ott (*11*)	5	7.5	67	1	1.1	91	Respiratory	1	0.3	333
	Subcohort, ≥ 15 yr latency	2	2.6	77	1	0.5	200	Respiratory	1	0.2	500
TCE	Axelson (*12*)	49	62.0	79	11	14.5	76				
	Subcohort ≥ 10 yr latency, high exposure	8	7.6	105	3	1.8	167				
EDB	Ott (*15*)	36	32.5	111	7	5.8	121				
	Subcohort ≥ 15 yr latency	26	21.8	119	6	4.3	140				
TCE PCE CCl_4	Blair (*13*)[a]	330	330	-	87	67.9	1.28	Lung bronchus	17	10.0	1.7
								Cervix uteri	10	4.8	2.1
								Kidney	2	1.0	2.0
								Skin	3	0.7	4.3
								Leukemia	5	2.2	2.3
								Digestive	25	18.0	1.4
TCE	Blair (*14*)[a]	1292	1292	-	244	223.7	1.09	Esophagus	10	5.4	1.9
								Liver	10	6.1	1.6
								Lung	62	56.7	1.1
								Digestive	86	72.6	1.2

[a]Relative risk.

Mortality patterns among dry cleaning and laundry workers, potentially exposed to CCl_4, TCE, PCE and petroleum solvents, were studied by Blair et al. (*13*) and analyzed by the proportionate mortality method. The age-, race- and sex-specific cause of deaths for persons in the U.S. between 1957 and 1970 served as the comparison. A significant excess of cancer mortality was observed, with 87 cancer deaths observed and 67.9 expected. Malignancies of the respiratory system, skin and uterine cervix were significantly elevated. Because these workers were exposed to multiple substances known to be carcinogenic, it is difficult to attribute this excess to one substance.

Blair (*14*) recently reported the results of a proportionate mortality study of workers in the metal polishing and plating industry. These workers were potentially exposed to various metals, corrosive and caustic alkaline solutions, and solvents such as TCE and PCE. Mortality patterns among white male metal platers who died between 1951 and 1969 were compared with expected numbers based on cause-specific proportionate mortality for U.S. white males. Excess cancers of the esophagus and liver were present in the study population. Excess cancers of other organs, such as lung and digestive system, were not statistically significant. As with the dry cleaner population, exposures to more than one substance known to induce cancer experimentally do not allow the determination of any specific etiologic factor.

Ott et al. (*15*) reported on the mortality experience of 161 men exposed to EDB. Expected deaths were calculated from the U.S. white male general population. No excess of total deaths or total malignancies occurred. Of the total cohort, 86% achieved a latency of at least 15 years since first exposure. The number of cancer deaths in this study is too small to permit any valid inferences regarding the carcinogenic risk of the EDB exposed workers.

Of the substances reviewed, only the studies of workers exposed to ECH and to dry cleaning and degreasing solvents suggest an elevated risk of cancer. The excess liver cancer in the studies by Blair et al. (*13*, *14*) is noteworthy in view of experimental study results demonstrating the induction of liver cancer with the same industrial solvents to which these workers were exposed. The remaining studies report no significant excess of cancer mortality. However, it is apparent that each of these "negative" cohort studies did not consist of a sufficient sample size and latency period to permit any meaningful conclusion regarding carcinogenic risk. The probability of identifying an excess cancer risk in the study population, if in fact it is present, is referred to as the power of the study. The power for the cohort studies reviewed was calculated based on the methods of Cutler et al. (*16*) and Beaumont and Breslow (*17*). Table 4 shows the

Table 4. Observed and expected numbers of cancer death latency, minimum number of cancer deaths needed to insure statistical significance at the 0.05 level (one tailed-test) and the statistical power to detect a 1.5 relative risk.

Substance	Investigators	Site of cancer	Observed deaths	Expected no. of deaths at comparison population rate	Minimum no. of deaths required to conclude that study population rate exceeds comparison population rate[a]	Probability of concluding that study population rate exceeds comparison population rate when it is actually 1.5 times as high (power)[b]
ECH	Enterline (*8*),	All cancer	13	14.15	22	0.52
	Brown and Rinsky	Lung cancer	8	4.92	10	0.26
	(*9*) Greater than	All cancer	12	8.92	15	0.38
	15 yr latency	Lung cancer	7	3.46	8	0.21
ECH	Shellenberger (*10*)	All cancer	2	3.50	8	0.21
VDC	Ott (*11*)	All cancer	1	1.1	4	0.12
	Greater than 15 yr latency	All cancer	1	0.5	3	0.09
TCE	Axelson (*12*)	All cancer	11	14.5	22	0.53
	Greater than 10 yr latency	All cancer	9	9.5	16	0.40
EDB	Ott (*15*)	All cancer	7	5.8	11	0.29
	Greater than 15 yr latency	All cancer	6	4.3	9	0.24

[a]If the minimum number of cases is observed, the probability of incorrectly concluding that the study population rate exceeds the comparison population rate, when in fact it does not, is less than 0.05.

[b]Calculated as: $Z^{(1-\beta)} = 2n^{1/2}(R^{1/2} - 1) - Z^{\alpha}$, where R = relative risk, Z^{α} = upper 100α percentile of unit normal distribution, $Z^{(1-\beta)}$ = upper 100 $(1 - \beta)$ percentile of unit normal distribution, and n = expected number of cases.

observed and expected number of total cancer of lung cancer deaths, the minimum number of deaths needed to observe the respective significant excesses and the resultant power to identify a 50% increase in the risk. The data are calculated for the total cohorts and the subcohorts with 10 or more or 15 or more years since initial exposure, as indicated in the studies. In order to conclude that the rate of cancer in the study population is greater than the rate of cancer in the control population, the number of observed cancer deaths must equal or exceed the minimum number of deaths required, as calculated using the Poisson distribution. The power calculations were based on the ability to detect an increase of 50% in the overall cancer risk of the study population, i.e., a relative risk of 1.5. [Criteria established by OSHA (7) for adequate sensitivity and specificity of an epidemiologic study require the ability to detect a relative risk of 1.5 in site-specific cancer risk.] The power of each study was determined by using the expected number of cancer deaths generated by the respective comparison population rate. The power to detect a 50% increase in total cancer mortality for the entire cohort ranges from 0.12, as shown for the VDC study of Ott et al., (11) to 0.52 for the Enterline study of ECH (8) and 0.53 for the Axelson study of TCE (12). These calculations clearly illustrate that the probability of detecting a 50% increase in total cancer mortality was rather low. For the cohorts with 10 or more or 15 or more years of latency, the power to detect a difference is even less. If the more appropriate site-specific cancer risk is considered, the statistical power to detect a difference is still lower. These latter data are not presented.

Further calculations from data in Table 3 illustrate the site-specific insensitivity of these studies. Given the expectation of 0.2 respiratory cancer deaths as reported in the VDC analysis (11), an observed risk of tenfold would be required to achieve statistical significance. However, this would still be based on only two deaths from a common malignancy. Axelson et al. (10) outlined several limitations of their analysis of workers exposed to TCE. A twofold risk of total cancer mortality would have been required to demonstrate a statistically significant excess in their study population, the magnitude of which is rarely observed in cohort mortality studies. The authors concluded that "the cancer risk to man from TCE can by no means be ruled out from this study, particularly with regard to uncommon malignancies such as liver cancer." The authors further stated that had one case of liver cancer been observed, the relative risk for cancer at this site would have been 3.4 for the total cohort and 25.0 for the high exposure subcohort. As stated by OSHA (7), the group of exposed subjects must be large enough to permit detection at least a 50% increase in site-specific cancer incidence in comparison to the control population. Cohort mortality studies such as these do not meet these criteria and therefore lack the sensitivity and specificity to detect an excessive cancer risk.

Conclusion

Although experimental studies have now demonstrated the carcinogenicity and mutagenicity of VC related compounds, in general, epidemiologic studies available for review do not allow for the assessment of carcinogenic risk among humans exposed to these substances. This conclusion is based on the observation that all of the cohort studies reviewed lacked sufficient statistical power because of the small sample sizes. Furthermore, individuals were not followed over an adequate period of time to allow cancers to become clinically manifest.

Although information presented indicates that all of the substances studied are high production volume chemicals with large estimated numbers of exposed workers, the number of workers available for study who have achieved an adequate latency period is small. The retention of personnel records containing the information necessary for epidemiologic study of health hazards is not a requirement in the United States and adds to the problem of insufficient sample sizes available for study. On the basis of these observations, it is apparent that qualitative carcinogenic risk of a specific chemical substance to humans must be estimated through the conduct of experimental studies.

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Needs for Public Health Intervention and Needs for New Research on Vinyl Halides and Their Polymers: A Public Policy Perspective

by Dale Hattis*

Consideration of needs for public health interventions and new research requires comparative assessments of the health benefits that are likely to result from alternative uses of limited regulatory and technical resources. This paper briefly examines regulatory and research priorities in the light of recent information on the carcinogenic hazards of vinyl chloride and alkyl and vinyl halides related to vinyl chloride, the respiratory-system hazards of poly (vinyl chloride), and the reproductive hazards of vinyl chloride. Specific suggestions are made for relatively promising types of efforts in these areas.

Introduction

The papers presented in this conference represent a considerable expansion of available information on the hazards of vinyl chloride, poly(vinyl chloride), and vinyl bromide. There are also useful reviews of previously available literature on a broad range of other alkyl and vinyl halides. In this session, the focus shifts from the often slow and deliberate process of expanding what we "know" about carefully circumscribed questions in VC/PVC toxicology/epidemiology to what at first glance will seem a much more speculative process. Judgements must be made about appropriate priorities for regulation ("public health intervention") and for new research—and for purposes of making such judgements it is important not only to understand what we can be said to know today about a restricted set of well-researched hazards, but what is ultimately likely to be true and worth knowing about the whole range of alternative hazards which could be the targets of research and regulatory efforts.

For purposes of setting regulatory policies, we need to ask, "Where is there likely to be a relatively large amount of harm occurring which is likely to be relatively easily preventable by using the intervention tools at hand?" Some of the modes of intervention available either to OSHA or EPA for addressing different kinds of problems include: conventional OSHA time-weighted-average exposure limits for specific air contaminants, enforced by industrial hygiene inspections (best adapted to hazardous exposures which are concentrated in a few establishments with relatively large numbers of workers exposed per establishment, for most productive use of limited industrial hygiene inspection manpower); limitations on the manufacture or sale in interstate commerce of specific chemicals or formulations for specific high-hazard uses, under the Toxic Substances Control Act (best adapted to hazardous exposures which occur in dispersed locations in industry as a result of the use of specific industrial chemical products, e.g., degreasing and dry-cleaning solvents); efforts to redirect dosage away from unusually sensitive subgroups of workers or prevent effects by preventive medical surveillance, mandated in OSHA standards; and "generic policy" standards (e.g., the recent generic OSHA carcinogen policy) designed to facilitate standard-setting and stimulate "voluntary" corporate action in ad-

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vance of standard-setting for a range of hazards deemed to pose similar types of issues for public policy.

For purposes of assessing priorities for research relevant to public health, we need to ask, "Where is there an opportunity to significantly reduce uncertainties in the benefits of candidate public health intervention measures, using the research tools at hand?" The relevant research tools here include not only toxicological and epidemiological research into likely health effects, but also technological research on control methods and innovative development of safer industrial processes.

The present paper will attempt to address these questions of regulatory and research needs in the light of recent information on three topic areas that are the subjects of this conference: the carcinogenic hazard of vinyl chloride, and alkyl and vinyl halides related to vinyl chloride, the respiratory-system hazards of poly(vinyl) chloride and the reproductive hazards of vinyl chloride. Through the details of these separate subjects, there is one theme that will emerge—both scientists in considering research opportunities and policy makers in considering public health interventions need to structure their efforts to have the widest possible application. Policy makers must seek sensitive points of leverage in the world, where a limited intervention may be expected to produce substantial health benefits for a large number of people. Scientists must seek the critical experiments which contribute to the establishment of generalized rules or principles, with application to the widest possible set of questions of public health significance.

Carcinogenic Hazards of Vinyl Chloride and Related Compounds

Does the information that has become available over the last few years suggest that a new round of public health initiatives to further reduce the eventual incidence of vinyl chloride cancers is likely to achieve greater health protection benefits than alternative uses of the same technical, standard-setting and enforcement resources? In order to give an affirmative answer to this question, it would be necessary (though not necessarily sufficient) for us to draw two conclusions from available information about vinyl chloride: (a) that there is a substantial chance that long-term exposure to vinyl chloride at the current standard level of 1 ppm poses an appreciable risk, and (b) that a new round of OSHA standard setting and enforcement would lead to substantial reductions in current average worker exposures to vinyl chloride.

With respect to the first question, I think there is substantial basis for concern that the current 1 ppm vinyl chloride standard may pose an appreciable carcinogenic risk to workers. As part of a 1976 retrospective assessment of the benefits and costs of the original OSHA 1 ppm standard (*1*), my colleagues and I made projections of likely human risk based on the available data from Dr. Maltoni's BT1 (rat) and BT4 (mouse) results (*2*), an assumption of linear dose-response kinetics at low doses, and four alternative sets of rules for translating the rodent vinyl chloride dosages to equivalents for human workers. (Basically, the four alternative rodent/human extrapolation rules arose from the four permutations of the choice between expressing dosage as milligrams/body weight vs. milligrams/body surface area and the choice of whether or not to divide the rodent dosage by 35 to adjust for the 35-fold difference between rodent and human lifespans.) These projections suggested that a year of worker exposure to vinyl chloride at the current OSHA 8-hr limit of 1 ppm might be expected to lead to an additional cancer risk from all tumors of between 1×10^{-4} and 3×10^{-2} for the four different extrapolation rules. Even the lower of these figures implies that some tenths of a percent of workers exposed over an appreciable portion of a working lifetime at the standard level may expect to develop an occupationally related cancer; if one of the more pessimistic (higher) extrapolation rules should prove more nearly correct, the ultimate toll might well be in the tens of percent for long-exposed workers.

On examination of the more complete animal carcinogenesis data presented by Dr. Maltoni, it appears that projections of roughly the same order of magnitude would be made based on the more recently available information. The one possible exception is the appreciable excess of mammary cancer which appears to persist at relatively low exposure levels.

Data from studies in humans modify this picture slightly. The preliminary epidemiological information which is available to date does not seem to be indicating as large a risk among workers exposed to vinyl chloride in the past as might be expected under the more pessimistic extrapolation rules from the animal data. For example, the best guess one might make from the data of Dr. Weber for German chemical industry workers with and without exposure to past high levels of vinyl chloride is that the vinyl chloride workers appear to show an excess of deaths from all malignancies amounting to something like 6% of the total deaths which have occurred so far in that cohort. It should be stressed,

of course, that because of the decades-long latency period for most occupational cancers, it is likely that the final percentage of past vinyl chloride-exposed workers who develop occupational cancers will be higher than that observable among the deaths which have occurred to date.

In sum, prudent people in both government and industry must consider that a real chance remains that chronic worker exposure at the level of the current 1-ppm standard may carry an appreciable cancer risk. As new production and control technology become available over the coming years there should be a regular, continuing program to implement superior processes and reduce worker exposure as far below 1 ppm as is technically feasible. Available data suggest that the Swedish PV polymerization industry is now operating with average worker exposures in the range of 0.2 to 0.3 ppm (*3*). My impression from talking with OSHA industrial hygienists and from the observation that as of 1976-77 over 90% of vinyl chloride samples from OSHA inspections were in compliance with the 1 ppm standard (*4*), is that this kind of performance may also be being achieved in the U.S.

I think it is doubtful, however, that a new round of formal OSHA standard-setting on vinyl chloride would represent the most productive use of the agency's limited resources at this time. Even within the family of alkyl and vinyl halides which have been discussed at this conference, there are materials which,even if they prove to be some orders of magnitude less potent as carcinogens than vinyl chloride, are likely to yield greater public health benefits from intervention. The PVC polymerization industry has several thousand workers, exposed to vinyl chloride on average in the range of tenths of a ppm. Because of the major pressures placed on the vinyl chloride/poly(vinyl chloride) production industries over the past several years, it seems unlikely that there are still many available but unexploited techniques for making further order-of-magnitude reductions in exposure. On the other hand, the number of workers in the dry cleaning industry is in the hundreds of thousands (*5*), and available data indicate exposures to perchloroethylene in the high tens and low hundreds of ppm (*6*). Metal degreasing operations may offer another similar picture with respect to exposure to trichloroethylene. Solvent and chemical intermediate uses of ethylene dichloride and pesticidal and fuel additive uses of ethylene dibromide may also place substantial numbers of people at risk in situations where many of the relatively easy technical measures to reduce exposures have not yet been implemented. Even though the available data on the carcinogenicity of some of these materials is not as conclusive as for vinyl chloride, and relative potencies are highly uncertain, the dangers of widespread cancer and related risks and likely untapped opportunities to control exposures suggest that they should be placed relatively higher on OSHA and EPA priority lists for public health interventions than vinyl chloride.

After this extended discussion of intervention priorities it will perhaps not be surprising that I see the importance of further scientific work on vinyl chloride primarily in terms of its potential to produce generalizeable lessons for quantitative animal-to-human extrapolations, to advance understanding of the dynamics of metabolism of precursor substances to active carcinogenic intermediates, and to provide a set of reasonable technical expectations relevant to future risk assessments for chemicals related to vinyl chloride.

The epidemiological observations on worker groups with previous exposure to vinyl chloride clearly need to be pursued in future years. However, in the future, much more disaggregated data should be made widely available for analysis using different approaches for separately assessing the effects of duration of exposure, calendar year of exposure, age at which exposure occurred, relative level of exposure and years of follow-up relative to the years of exposure. Because of the observed "saturation" of some vinyl chloride tumor responses observed in animals (*2*), it is important not simply to assume in analyzing the epidemiological data that high-level short-term exposures will have the same effects as low-level long-term exposures that deliver the same total dose.

Epidemiological observations on the large worker groups exposed to dry cleaning solvents have already yielded tentative indications of excess cancer incidence in some cases (*7*). Further ongoing epidemiological work on these populations is clearly of major importance. In preparation for possible positive findings in these efforts, I think it would be prudent now to foster creative technological development work to understand the options for alternative dry cleaning/degreasing solvent systems and equipment to make large reductions in worker exposures, should that be eventually called for.

Finally, further observations in animal systems should seek biochemical explanations for the ways in which the quantitative vinyl chloride carcinogenic response changes with dosage, animal strain and bodily tissue. Given such knowledge, comparative studies with other alkyl and vinyl halides may provide better quantitative guidance on likely carcinogenic dose response curves for this whole family of related chemical agents.

Respiratory-System Hazards of Poly(vinyl Chloride)

The elegant study presented by Dr. Seaton, supported by the studies and case reports of other workers, indicates quite clearly that long-term exposures to fine PVC dust (less than 5-10 μm in size) can lead to chronic declines in standard measures of lung function. In considering public health interventions based on these results, I would suggest again that two questions be asked: (a) do the present data give us reason to suspect that fine PVC dust is much more hazardous per unit of exposure than other miscellaneous organic and inorganic dusts with comparable partical size ranges that are not regulated under OSHA's "nuisance dust" exposure standard, and (b) how extensive is the PVC dust problem likely to be relative to the problem posed by other particulates.

Taking the latter question first, it appears from the presentation of Dr. Wheeler on poly(vinyl chloride) processes and products that PVC preparations with predominantly small particle sizes are mainly produced by a relatively small sector of the industry that uses the "emulsion" polymerization process. Given this, and the possibility that even for this sector of the industry in the future, much of the material could be marketed in wet form now that the dust hazard is becoming recognized, it seems likely that a coercive intervention aimed specifically at fine PVC resin producers and consumers might yield relatively small benefits.

On the other hand, the problem of exposure to miscellaneous "nuisance" dusts in general is clearly common in many different industries. I think it is likely that a general reappraisal of policies and standards with regard to miscellaneous particulates in respirable size ranges might well lead to significant long term benefits in the prevention of chronic pulmonary impairment. To build an appropriate database for such a reappraisal, I would suggest that in conjunction with the next round of NIOSH's National Occupational Hazard Survey, there should be a cross-sectional survey of lung function among workers exposed for many years to various kinds of respirable particulates (controlling, of course, for past smoking habits and other relevant factors). Based on the results of such a survey and other relevant data, policy-makers could determine what regulatory distinctions should be made between different kinds of fine particulate matter. At the very least, it seems likely that the term "nuisance" as applied to miscellaneous dusts should be done away with if, as I suspect, there is a general observation that long term exposures to fine particulates is associated with an increased risk of impaired lung function.

Before leaving this subject I would like to make one additional plea to researchers doing epidemiological work on potential chronic respiratory hazards. For purposes of policy analyses on possible standards, it is vital that data be presented not only in terms of average losses in lung function among populations as related to exposure and age characteristics, but also in terms which allow the full reconstruction of the population distribution of lung function values as related to exposure and age. Potentially important changes at the tails of population distributions of lung function may be obscured unless the basic regression analyses which determine average effects are supplemented by presentations which reveal what is happening to subgroups which for other reasons have better or worse lung function than average.

Reproductive Hazards of Vinyl Chloride

For this area too, it seems to me that an effort to resolve the general issues posed by reproductive hazards in the workplace and set a "generic policy" standard will be likely to have greater long term public health benefits than an attempt to promulgate a standard which is narrowly focussed on the reproductive hazards of vinyl chloride. There are some very important general issues which need resolution, and the educational effects of the policy-making process alone could have substantial widespread beneficial effects through changes in current practices in industry.

Beyond the reduction of exposures—which should be pursued to the maximum extent feasible—designing appropriate medical surveillance and compensated removal programs for workers exposed to reproductive hazards is a very delicate and controversial subject. Many women, in particular, are justifiably fearful that newly won employment opportunities may be eroded and that attempts to eliminate women with child-bearing potential from employment in specific jobs have the effect of reinforcing the old notion that women's primary function in society is to make babies. Cases of real abuse in company medical removal policies have been alleged in the lead industry in which some women have apparently felt forced to choose between their jobs and undergoing sterilization operations.

Adding to the concern of women over unequal treatment has been the fact that male mutagenic

risks have not received the same level of attention with respect to medical removal as have female teratogenic risks. Exposure of reproductively active males to mutagens is thought to generally pose greater mutagenic risks than exposure of females, because male reproductive cells divide continuously throughout life, whereas female reproductive cells do not usually divide after birth until fertilization. In epidemiological studies of mutation rates for point mutations, mutagenic risks generally show a stronger positive correlation with paternal age than with maternal age (*8*).

I believe that with care and sensitivity to these issues, it is possible to design medical removal protection programs which reduce teratogenic and mutagenic risks while not infringing on individual rights or other social values. A reasonable general approach could include a full and frank disclosure to all exposed workers of the known and suspected mutagenic and teratogenic risks of the substances with which they are working. Removal, with economic protection, at the worker's option, should be triggered by the intention of the worker to have children, sufficiently in advance of conception to allow the substance(s) of concern to be eliminated from the body before the critical events which occur in each sex. For prevention of mutagenesis in males, reduction of the body burden of the substance of concern to the desired protective level should occur some months before conception, to allow sensitive postspermatagonial stages in the development of sperm to be purged from the system. Return to the previous job can be safely permitted after conception is confirmed, provided that precautions are taken against transport of the hazardous substance home on the worker's clothing. For prevention of teratogenesis in pregnant women, reduction of the substance of concern to the desired protective level should occur prior to conception. Return to the previous job should probably wait either until the completion of the pregnancy or the completion of lactation, depending on an assessment as to whether the substance poses hazards to the child by way of the mother's milk.

In conclusion, I would like to reiterate, that in considering priorities both for public health interventions and for research, it is often helpful to step back a few paces from the immediate problems at hand. With careful consideration of the generic issues posed by specific problems related to vinyl chloride, I think both scientists and policy makers alike can direct their efforts toward projects with greater payoff than would be realized by straight forward extensions of previous efforts.

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Contributed Articles

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Process-Dependent Risk of Delayed Health Effects for Welders

by Richard M. Stern*

In most industrialized countries large numbers of workers are exposed to welding fumes. Although the general pattern of welders' health may not significantly differ from that of workers in other dusty industrial occupations which demonstrate elevated incidence of respiratory tract diseases with long latency periods, the extremely wide range of substances at potentially high concentrations produced by various welding technologies may give rise to undetected process-specific high-risk working conditions: ("hot spots"). The origin, prevalence and range of magnitude of such hot spots, especially for cancer of the respiratory tract, is discussed, with emphasis placed on the assessment of risk resulting from exposure to Cr(VI) and Ni accompanying the use of various technologies for the welding of stainless and high alloy steels. The wide variation of health effects found within the industry, however, indicates the need for a standard protocol for future epidemiological studies, as well as for the development of suitable methodologies for experimental risk assessment.

Introduction

The use of welding as a technology for the joining of materials occurs worldwide, engaging of the order of 0.2-2% of the working population in typical industrialized countries. The major processes have been in universal use for of the order of 50 years, and materials and hence exposures have been shown to be, under similar circumstances, comparable throughout the world. The technology is extremely labor-intensive, labor accounting for 80-90% of production costs for all but the most modern automatic processes. However, new processes with higher productivity having an increased range of applicability are continuously being introduced. Since these demonstrate typical doubling times (in terms of their absolute use) of 7-10 years, depending on the details of the economic growth in the individual country, some processes which currently account for significant worker exposure were relatively rare 20 years ago.

The nature of the technology is such that, whenever an arc is struck, the resulting high temperature which melts both work piece and consumable wire or rod produces significant amounts of vaporized metal and (where present) slag formers and flux, which condense in the rising plume of heated air to form a high local concentration (upwards of 100 mg/m^3) of a complex mixture of gases, oxides and other compounds, whose chemistry is determined by the technology, materials and welding parameters used in each case.

The possibility of high, localized concentrations of a wide variety of biologically active substances which in turn have a wide range of toxicity [e.g., O_3, NO_2, Cr(VI), V, As, Mn, Ni, Be, Cu, Na, K, Si, F, Pb] represents a potential source of health risk to significant numbers of workers throughout the world. The magnitude of actual risks which occupational exposures represent are however largely unknown and uninvestigated. Since the fume concentrations of various substances vary a millionfold from process to process, and since individual exposure can depend to a large extent on job situation, one can anticipate that the average risk arising from welding, for a given welder, or any given welding population, and therefore for the welding industry as a whole, is not homogeneous but is made up of a range of process and job-specific risks whose order of magnitude could be estimated by a proper risk assessment (*1*, *2*), based on knowledge

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of the range of process and job specific exposures involved.

The observation of a wide range in the nature and degree of health effects among welders using similar technologies in different localities, and between local users of different technologies indicates that a number of variables determine exposure and hence actual risk, even within a given welding process. Any attempt to reduce occupational health risk must therefore be based on an understanding of these parameters, and the way in which they might affect the nature of the material produced (e.g., the chemistry of the consumables), the rate at which fume is generated (e.g., the values of the welding variables; voltage, polarity, current, arcing time), the local fume concentration (e.g., type of ventilation) or the background exposure (e.g., workshop mix of technologies and applications).

Welders could be used as suitable model populations for studies of process or occupation dependent risk provided one has a knowledge of: (a) the magnitude of available populations and their distribution among various technologies, (b) the types of exposures appropriate to these subcohorts and (c) the techniques necessary to estimate the origin and magnitude of risk accompanying each class of exposure. One useful approach to establishing the necessary methodology is to attempt to identify specific job situations which might be associated with high degrees of excess risk, i.e., process-dependent "hot spots."

Distribution of Welding Populations

Types of Processes

There exist approximately 20 major technologies within the welding industry which are used on ten major classes of materials providing the possibility for of the order of 5000-10,000 different working environments due to the possible variations in composition of workpiece, consumables and welding variables.

Manual metal arc welding (MMA) uses short lengths of electrode coated with a complex material which provides for flux, slag and protection from oxidation through its melting and decomposition. Ten major electrode producers, each offering 100 different electrodes, which can be welded with three types of polarity (AC, ±DC), on several types of joints, account for 3000-5000 separate exposures which differ from each other by a factor of two or more in the absolute concentration of at least one of the 14 major chemical constituants of welding fume.

Metal inert gas welding (MIG) uses a continuous wire electrode and an inert gas (e.g., argon) which provides a shield against oxidation. For some classes of materials, an active gas (e.g., CO_2, O_2) is mixed with the inert gas to provide better surface properties (MAG process).

Tungsten inert gas welding (TIG) uses a nonmelting electrode and occasionally extra filler material.

Gas welding uses an oxy-acetylene or similar flame to melt the work piece.

Submerged arc welding (SA) uses a fully automated process where the arc is maintained under a covering of powdered flux.

In spot welding, material is joined by local resistive heating (provided by a transformed current pulse) under electrode pressure.

Cutting, burning and air (arc) gouging are processes involving the preparation of work pieces and are frequently performed by welders, their assistants, or special workers within the same trade.

The major classes of materials are: mild steel (MS), an alloy of iron, carbon, silicon, and occasionally molybdenum or manganese; stainless and high alloy steel (SS), containing iron, nickel, and chromium, and occasionally cobalt, vanadium, manganese, and molybdenum; aluminum (AL), either pure, or as an alloy with magnesium, silicon and/or occasionally chromium.

Distribution of Welders

Worldwide distribution of welders among the different technologies and their applications is difficult to determine directly because the average number of welders per firm is small (of the order of ten), and a large fraction (30-50%) of individuals exposed to welding fumes are not full-time welders but are also employed in allied trades. The best indirect method of estimating national welding populations is to determine the local use of welding consumables and assume 500 kg of electrodes and 2500 kg of wire per man-year for MMA and MIG welding, respectively. Unfortunately the competitiveness of the market for electrodes tends to make such information a trade secret, but from unpublished trade figures it is possible to estimate the distribution in more common categories, as is shown in Table 1.

Two countries, Sweden and Germany, have recently conducted detailed surveys of their welding industries. The results presented in Table 2 show that there exist wide international variations in the relative distribution of weld ing activity by technology and material. In general, however, the five combinations, MIG/MS, MIG/SS, MIG Al, MMA/MS, and MMA/SS account for between 60-70% of all welders.

Table 1. Distribution of welders by country for various processes

Country	Process	No. of welders		
		Stainless steel	Other	Total
Sweden, 1974[a]	MMA	5,400	18,600	24,000
Holland, 1978[b]		3,500	31,300	34,800
Japan, 1978[c]		80,000	350,000	430,000
U.S.A., 1976[d]				500,000
Germany, 1970[e]		13,000		97,000
Norway, 1978[b]		1,200 (?)		21,000
Great Britain, 1978[b]		10,000 (?)		87,000
Spain, 1978[b]		1,600		57,000
France, 1978		9,000		81,000
U.S.S.R., 1980[f]				1,500,000
Sweden	MIG + MAG + TIG	3,100	10,000	13,200
Holland				1,460
Japan				30,000
U.S.A.		1,900	57,000	58,900
Germany				66,000
U.S.S.R.				200,000
Sweden	Sub.			780
Holland	Arc			
Japan				15,000
U.S.A.				10,000
Germany				
Sweden	Other			
Holland	(incl. gas)			
Japan				1,000
U.S.A.				
Germany				106,000

[a]Data of Ulfvarson (3).
[b]Data of van der Sluis (4).
[c]Data of Masumoto et al. (5).
[d]Data of Jefferson (6).
[e]Data of Flemming and Sossenheimer (7).
[f]Estimated.

Process-Specific Welders' Exposure

Each technology produces a unique type of aerosol, of which 80-90% of the chemistry is determined by the composition of the consumable material, which is chosen to be metallurgically compatible with that of the work piece. To a first approximation, five combinations of the processes described above with various materials provide upwards of 70% of the total exposure, listed in order of complexicity of fume composition as follows: (a) MIG/AL: aluminum oxide, ozone; (b) MIG/MS (MAG MS): ferric oxide, manganese, silicon, copper, nitrogen dioxide; (c) MIG/SS: same as MIG/MS plus nickel, chromium, ozone; (d) MMA/MS: same as MIG/MS plus sodium, potassium, molybdenum, fluorine, titanium, calcium, aluminum; (e) MMA/SS: same as MMA/MS plus chromium, nickel, vanadium. (Approximately 40% of MMA/MS welding is performed on plates coated with shop primer, producing in such cases an additional 1-5% organic gas due to the pyrolytic decomposition of the epoxy or other polymer binder: welding fumes are otherwise usually free of organic material. Cutting and gouging provide high exposures to the oxides of iron, carbon and nitrogen and occasionally to zinc, tin, lead, and/or barium).

The amount of fume produced per unit time depends on the choice of welding parameters (current, voltage, wire dimensions, etc.) and the welders' exposure is additionally influenced by the actual job situation and degree of ventilation and/or fume exhaust provided. The approximate cumulative distribution of workplace exposures to total fume for the major technologies is shown in Figure 1. Shop background levels (BG) are also given.

The curves shown are only valid between 15 and 85% and appear to be representative for the trades indicated, data from Sweden, Denmark and the U.K. agreeing to within about a factor of 2. The use

Table 2. Distributions of Swedish welders by process and material.[a]

Process	No. of welders				
	Total	Mild steel	Stainless steel	Al	Other
MMA	25,585	16,854	5,896	1,496	1,339
MIG + MAG	9,143	6,232	1,594	1,141	176
TIG	4,216	1,541	1,529	913	233
Gas	3,823	2,762	479	325	257
Sub. Arc	783	540	210	32	1
Total	43,550	27,929	9,708	3,907	2,006

[a]Adapted from Ulfvarson (3). The German data, although unavailable for publication in detail (8), indicate that, while in 1980 the total number of welders has remained essentially unchanged from 1970 (see Table 1), there has been a reduction of about 25% in the number of MMA/MS welders and a corresponding increase in the number of welders using semiautomatic metal-gas techniques in this decade. Note that in Sweden the ratio of MMA to MIG/MAG/TIG welders is aproximately 2:1, while in Germany it is currently 1.1. Similarly 9% of the Swedish welding population works on aluminum alloys while only 3–4% of German welders are engaged in these processes. The data generally agree with estimates made based on consumable sales in the individual countries, assuming approximately 500 kg electrodes and 2500 kg wire per man year of MMA and MIG/MAG welding, respectively.

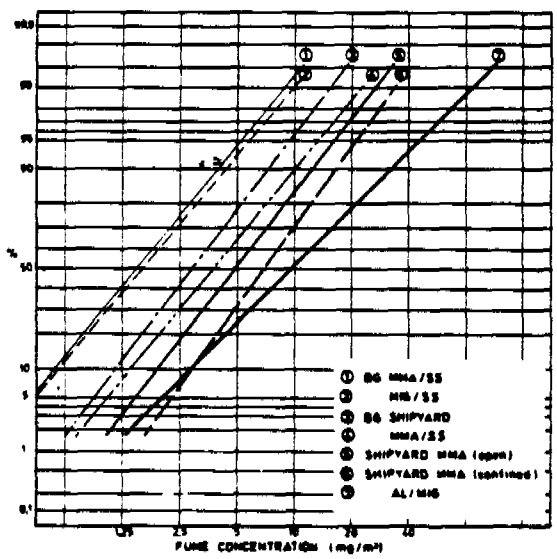

FIGURE 1. Cumulative distribution of working place exposures (%) vs. fume concentration (8 hr average) (mg/m³) for stainless steel and aluminium welding (in Sweden) and shipyard welding (in Denmark), including background levels (BG), liberally interpreted from Ulfvarson (3) and Beck Hansen (9).

of point extraction will reduce the average levels by approximately a factor of two to three (3). Note that for some applications a significant fraction of welders is exposed above 5-10 mg/m³: levels above 100 mg/m³ have been occasionally reported.

Because of local variations in consumable composition and distillation effects in the arc which can cause enrichment of the fume by as much as a factor of 100 for volatile components, it would be extremely difficult to make an a priori prediction of exposure to the individual elemental components of the fume based only on a knowledge of the process technology and work piece composition. Fortunately, however, a great deal is known about the amount and chemistry of welding fumes produced from individual electrodes and processes, and the variations thereof. A comparative study of MMA/MS fumes produced under standardized conditions by Danish, Dutch, British and Swedish welders (10) shows that locally, a welder or group of welders produce an amount of fume per unit time for a given electrode which varies by less than 3% within 95% confidence limits, when well supervised, and which varies by less than 18% (95% limits) when unsupervised. National average fume production rates vary by 3% from each other, when corrected for differences in the welding parameters actually used. Variations arise because a given electrode can be welded over a range of currents and voltages. Useful welds can be produced over a range of current of a factor of two, resulting in factor of two variation in burning rate and hence in specific fume production rate. Similarly, fume production per unit electrode length is proportional to arc length (and therefore voltage) which also can vary by a factor of two. Hence absolute fume production rates (and therefore concentrations and exposures) at maximum currents and voltages are approximately four times those at minimum values of the welding parameters. In addition, extreme variations in welding parameters can result in a variation of about ±40% in the relative concentration of the major fume components: Trace elements (< 1% concentration) can show much larger variations.

The results of laboratory measurement (10) of total fume and elemental concentrations resulting from the welding of a series of representative tech-

Table 3. Average concentrations of important toxic substances for a representative selection of welding processes.

	Steady-state concn in 10 m³, 3–5 kW, 25 sec per air exchange, t = 1 sec									
	Ozone concn (20 cm from arc, t = 1 sec), ppm[a]	Ozone, ppm[b]	Fume, µg/m³	NO_2, ppm	Cr(VI), µg/m³	Ni, µg/m³	As, µg/m³	Cu, µg/m³	Pb, µg/m³	Mn, µg/m³
TLV	0.1	0.1	5000	0.3 [c]	1.0[d]	15[d]	2	200	150	800[e]
Ceiling limit	0.3	0.3		1.0						
Process										
12.51, A, MIG/MS	0.22	0.8×10^{-6}	15000	0.12	1.5	15	1.5	30	1.5	470
12.51, A + CO_2, MAG/MS	0.15	0.8×10^{-6}	17000	0.015	0.5	1.5	0.5	50	3.0	1700
12.51, CO_2, MAG/MS	0.55	2.8×10^{-5}	12000	0.048	0.5	1.5	1.2	48	4.0	840
FF11, CO_2, MAG/MS[f]	0.88	4.2×10^{-5}	25000	0.23	1.0	5.0	2.0	75	8.0	4000
3RS17, MIG/SS	0.31	5.6×10^{-5}	5000	0.23	35	250	0.5	30	5	350
16.15, A, Al/MIG	0.39	7.1×10^{-5}	22000	0.14	20	0.5	—	1	4	—
16.04, A, Al/MIG	0.72	3.3×10^{-5}	22000	0.11	0	0	—	—	—	—
16.01, A, Al/MIG	0.88	—	28000	0.06	4	1	—	—	—	—
OK 48.15, MMA/MS[g]	—	—	10000	0.02	2	—	5	10	3	350
P 316, MMA/SS[h]	—	—	10000	0.02	300	50	—	30	8	270
PK 46.16, MMA/MS[h]	—	—	10000	0.02	3	1	3	30	3	500

[a]Removal of fume will result in a longer time constant t and an increase in these values by a factor of 2–10; t = halflife in standard welding fume.
[b]Calculated from near zone (r < 20 cm) only; practical levels will be higher by a factor of 2–5.
[c]Proposed, NIOSH.
[d]Proposed NIOSH limits for carcinogens.
[e]Change in 1980 from 5000.
[f]Low hydrogen.
[g]Rutile-basic.

nologies produced under comparable, standard conditions (3-5 kW) are presented in Table 3. The values are the estimated steady-state concentrations to be found in a 10 m³ volume with an air exchange every 25 sec. Ozone concentrations depend on the half-life for this reactive substance, which is in turn determined by the amount and nature of the fume present. For the sake of simplicity, it will be assumed that these few processes are representative for the industry, and these fumes can be considered as surrogates for those comprising the major exposures of welders.

By combining the data of Figure 1 with those of Table 3, it is possible to estimate the relative fraction of welders engaged in a particular trade whose exposure will exceed a given Threshold Limiting Value (TLV), and who by definition can be considered to be at "administrative risk." The fraction of populations at administrative risk for different substances, as a function of technology and material are shown in Table 4. In general, the majority of exposures to other elements do not exceed the respective TLV values provided the TLV for total fume is not exceeded.

The estimates of Table 4 are based on the average elemental concentrations of the surrogate welding fumes listed in Table 3. If one considers all the common consumable types within each major category, which are available industry wide, then a given elemental concentration for a class of fume can vary by a factor of three from these "average" values. In spite of such variations, examination of available data (*1-3*, *11*) such as presented in Table 3 permits separation of welders into cohorts having average exposures which can be expected to be distinct with respect to the presence or absence of certain characteristic substances, and hence which might result in unique health risks.

The Health of Welders

Pneumoconiosis and Siderosis

The extremely rich literature of case histories, health surveys, and hygienic measurements in the welding industry has recently been catalogued (*2*). The generalized risks of welding are indicated by reports of cases of accidental death due to electric shock, and occasional acute and sometimes fatal intoxification due to inhalation of high concentrations of Cd, ozone and oxides of nitrogen, and manganese; metal fume fever due to exposure to

Table 4. Estimated fraction of welders at administrative risk, defined as those exceeding the TLV for various substances as a function of the process.[a]

Substance	TLV	Source	Process	Welders at risk, %		
				Mild steel	Stainless steel	Aluminum
Total fume, $\mu g/m^3$	5000	NIOSH accepted	MMA[b]	75	45	
Ni, $\mu g/m^3$	15	NIOSH proposed, 1980 (carcinogenic)			75	
Cr (VI), $\mu g/m^3$	10	NIOSH, probable, 1980 (carcinogenic)			98	
Mn, $\mu g/m^3$	800	NIOSH, in effect, 1980		10	5	
NO_2, ppm	0.6	NIOSH proposed, 1981		10 (?)	20	
Total fume, $\mu g/m^3$	5000	NIOSH accepted	MIG		8	90
Ni, $\mu g/m^3$	15	NIOSH proposed, 1980 (carcinogenic)			30	
Cr (VI), $\mu g/m^3$	10	NIOSH, probable, 1980 (carcinogenic)			75	
Mn, $\mu g/m^3$	800	NIOSH, in effect, 1980		60	5	
NO_2, ppm	0.6	NIOSH proposed, 1981			20	40
O_3, ppm	0.1	Accepted		2	20	40
Total fume, $\mu g/m^3$	5000	NIOSH accepted	TIG		8	1
Cr (VI), $\mu g/m^3$	10	NIOSH, probable, 1980 (carcinogenic)				8
Mn, $\mu g/m^3$	800	NIOSH, in effect, 1980			5	
NO_2, ppm	0.6	NIOSH proposed, 1981				5
O_3, ppm	0.1	Accepted		2	20	1

[a]Derived from Table 3 and Figure 1. The fractional populations shown to exceed TLVs can only be estimated; the relative fractions given are therefore uncertain to about 20% (with an absolute uncertainty of no less than 5% for the small values).
[b]Approximately 40% of all MMA/MS welders work on primed plates and are therby exposed to organic gases of unknown TLV having concentrations ranging from 1 to 5% of those found for inorganic solids.

Zn, Cd, Pb, Sn, and/or Cu appears to be common. Some risks are, however, obviously process-dependent: e.g., exposure during the welding of stainless steel in confined spaces to high concentrations of fume containing water soluble Cr(VI) has been reported to lead to acute and chronic chrome intoxification, dermatitis and asthma (*12-18*).

It is difficult at present to estimate the absolute incidence rates of these acute effects, since case reports are isolated and must be interpreted in terms of the 3-4 million man-years of welders' exposure accumulated annually in the countries whose literature is commonly cited. One might therefore examine epidemiological studies of welders in the hope of determining the absolute level of health effects. Several recent cross-sectional studies would appear to be based on sufficiently large local populations of welders to permit some quantitative determination of the effects of chronic exposure to welding fumes in several different localities and job situations.

A survey of the occurrence of (legally defined) pneumoconiosis (silicosis, asbestosis and silico-asbestosis) during the decade 1966-1975 has been conducted for the maritime-construction complex La Spezia which has a total work force of approximately 12,000 individuals, among whom are an undetermined number of welders (*19*). The relative cumulative incidence (in percent of all 951 cases) vs. exposure (in years) for the entire work force is shown in Figure 2. Approximately 50% of the total cases occur within 26 years exposure. The relative cumulative incidence for those 143 individuals identified as electric and gas welders is shown for comparison. The median response for this subcohort was at 23 years exposure. Since welders perform their activities throughout the maritime complex, they are exposed (as bystanders) to the same general atmosphere as the average work force, and therefore should have the same general pattern of disease, superimposed upon which is the effect, if any, of their specific welding activity. Since however neither asbestos nor crystalline silica appear in welding fumes, this incidence of asbestosis and silicosis among welders can only be due to bystander exposure. From Figure 2 it can be seen that the effect of welding would appear to be to accelerate by approximately 10% (i.e., 2-3 years) the onset of the pneumoconiosis characteristic for La Spezia, as detected among the welding population. Since the

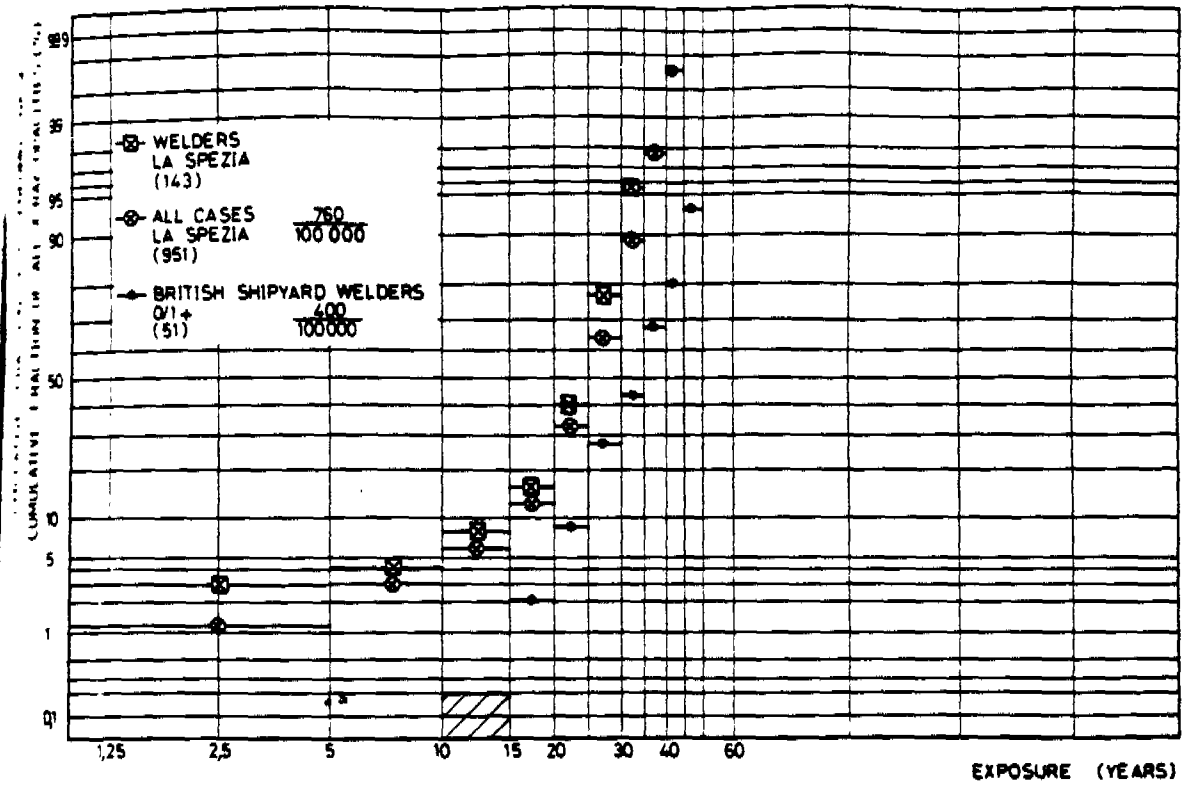

FIGURE 2. Fraction of total incidence of pneumoconiosis (%) vs. length of exposure (years) for the total workforce in La Spezia as well as for the welding subpopulation. Also shown is the fraction of total incidence of small round opacities (1 mm or greater) vs. length of exposure (years) for British shipyard welders.

relative size of the welding population appears to be unknown, the absolute incidence rate for their pneumoconiosis cannot be compared with that of the general shipyard population. It is however difficult to imagine that the numbers of welders with silicosis asbestosis compared to the entire group (143/951 = 15%) could be different from the ratio of welders to total exposed employees, without there being a significant variation in the respective incidence patterns. This conclusion is justified by the observations of a contemporaneous clinical study of randomly selected shipyard workers in Trieste which shows that welders exhibit a lower incidence of pleural changes (lesions and calcification: 10/37 = 7.3%, 2 137 = 1.5%) than the average of all shipyard employees (63/556 = 11%, 26/556 = 4.4%) who in general exhibit a 10-20 fold excess incidence of bronchopneumopathies compared to the general population (*20*).

In a second article (*21*), diagnostic chest x-rays from 661 British shipyard welders were examined by a panel of three readers to determine the absolute incidence of small round opacities of class 0/1 or higher (i.e., larger than 1 mm: "siderosis") as a function of welding exposure. The relative cumulative incidence for the 51 positive cases is plotted on Figure 2 as well. It can be seen the data follows a lognormal distribution, with approximately a 10 year median delay in detection of siderosis for British welders compared to the detection of pneumoconiosis in Italian welders, and that the low exposure tail appears to be missing. The British welders also worked in all sections of the shipyard, using a wide variety of processes, mostly MMA, but including MIG and TIG techniques (apparently absent in the La Spezia work experience).

The absolute cumulative incidence for siderosis vs. length of exposure among the British welders is shown in Figure 3: Data for a cohort of 220 (East) German welders (*22*) is shown for comparison. After the average length of employment of 17 years, approximately 1.6% of the British welders exhibit detectable x-ray mottling (caused by the local accumulation of welding fumes (mostly Fe_3O_4) having a high x-ray opacity). Doubling the exposure time results in a tenfold increase in incidence. The inci-

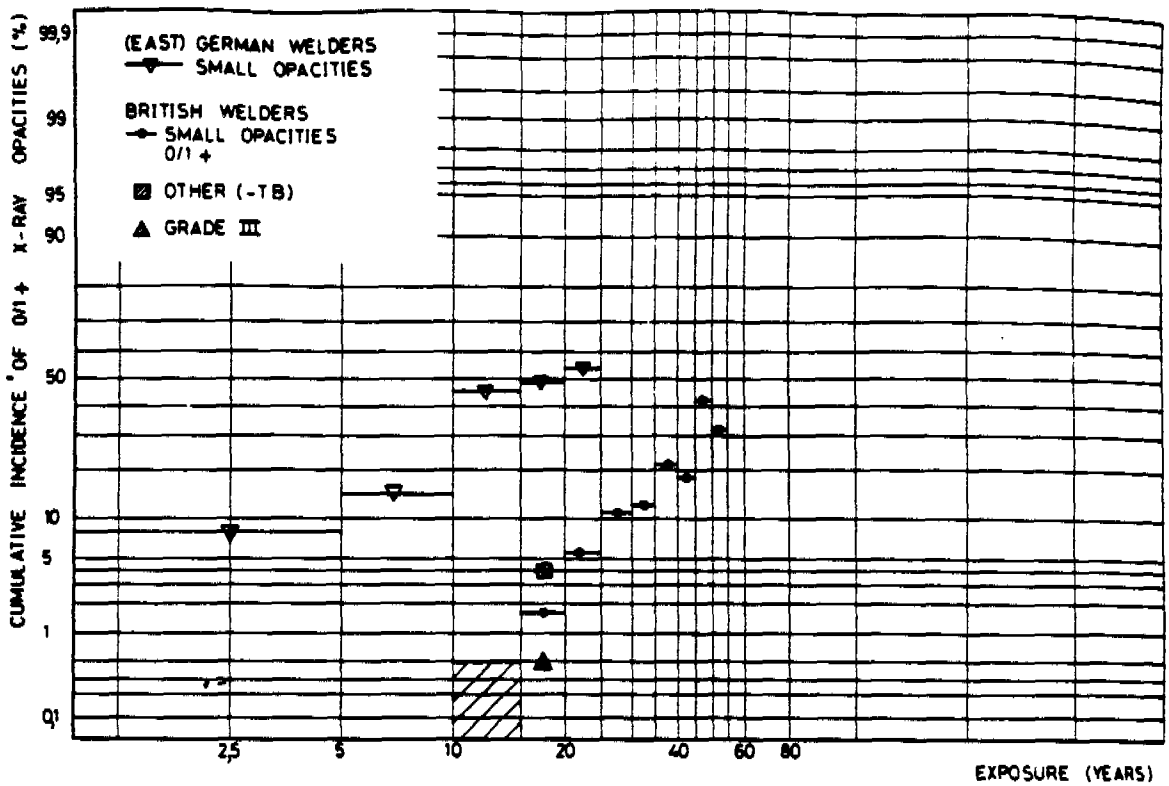

FIGURE 3. Fractional incidence of small round opacities (% of total cohort) vs. length of exposure (years) for British shipyard welders, and for siderosis for (East) German shipyard welders.

dence of other anomalies, and of grade III siderosis (opacities of 3 mm or greater) is also shown for the total population. The (East) German welders show a considerably different pattern of incidence of siderosis, with approximately 45% demonstrating detectable x-ray mottling after an average exposition of approximately 14 years: the incidence of grade III siderosis after this exposure is 1%.

Since the British welders are estimated to have exposure of approximately 5 mg/m^3, one can convert the length-of-exposure data to cumulative exposure (mg/m^3 years), as is shown in Figure 4. For comparison are shown the cumulative incidence data for silicosis for gold and for coal miners (*23*), since they represent the classic case of a lognormal dependence of cumulative incidence on total exposure. Average exposure levels in the East German shipyard would have to be 25-35 mg/m^3 for the incidence vs. cumulative exposure data to be comparable in the two cases.

The absolute incidence rates for siderosis for the British and (East) German shipyard populations were 400/100,000 and 1500/100,000 cases/man-year, respectively. The two studies are comparable however only if similar age distributions exist in both shipyards. British welders form a homogeneous group, having started work at age 17 with a universal apprenticeship, while the (East) German welders, who have an average age of 36 (compared to 34 for their British colleagues) commenced their working exposure at the average age of 23, some 6 years later, and presumably have some other type of early working experience. (The Italian working experience is very similar to that of the East German group.) The striking variation in siderosis incidence between the groups may have a number of origins: there is most likely a significant difference in exposure in the shipyards studied, but there might be significant differences in lung retention in the two cohorts due to age or genetic factors. It is also possible that criteria for reading thoracic x-rays may vary from country to country.

The siderosis discussed above, as found in shipyard and other welders is usually described as "benign", the x-ray mottling regressing after cessation of exposure in most cases (*24*). Some smaller

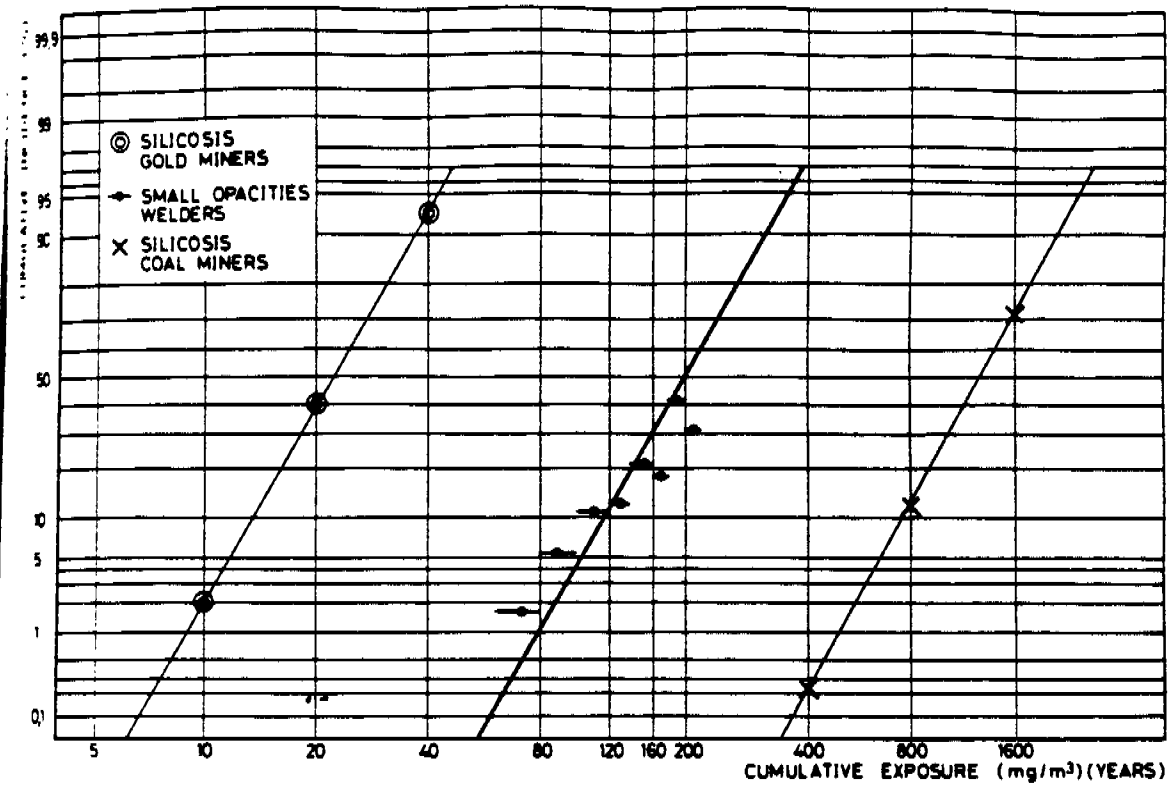

FIGURE 4. Fractional incidence of small round opacities (% of total cohort) vs. cumulative exposure to welding fume (mg/m³) (years) for British shipyard welders (assuming 5 mg/m³ average fume concentration). Similar lognormal behavior is found for coal miners and gold miners, each with a characteristic median exposure.

fraction of welders exhibits complex welder's pneumoconiosis characterized by irreversible changes including fibrosis (*17*, *25*) which may be due to specific welding exposure, particular individual sensitivity, or may be an expression of a bystander effect similar to that seen for the La Spezia welding population.

Most shipyard welding is done on primed plates of mild steel. Stainless steel welding is usually performed in shops dedicated to such activity. In one clinical study of 95 welders employed in an Italian metalworking shop using a wide range of technologies on both mild and Ni- and Cr-rich alloy steels, for those welders with more than 10 years experience only 8% show normal thoracic x-rays, 25% have normal respiratory function, and only 8% do not exhibit chronic bronchitis: all demonstrate squamous metaplasia of varying degrees (*26*).

Examination of the cross-sectional studies described above and others published in the literature of the past decade indicates that each subcohort apparently exhibits a health pattern characteristic for its own local working environment, to which a number of factors contribute. The fact that the welding cohort in one English shipyard exhibits approximately 8% abnormal thoracic x-rays (2% siderosis, 0.5% cancer, 3% tuberculosis, 4% other) while the cohort of a German shipyard exhibits 50% siderosis after the same length of employment is most probably an expression of different degrees of exposure to similar materials: productivity, arcing time, and electrode dimensions are probably higher, and ventilation poorer, in the East German yard, although this supposition can only be verified by direct measurement. On the other hand, the fact that 92% of welders in a workshop with mixed exposures to mild and stainless steels have abnormal thoracic x-rays, together with a high incidence of squamous metaplasia is more likely a reflection of the presence of metals such as Cr and Ni in the fumes from alloy steels, usually absent from the mild steels used in shipyard construction.

Pulmonary Function

Cross-sectional studies of pulmonary function, which should be more sensitive than clinical x-ray surveys for the detection of the effects of exposure

to welding fumes, are also difficult to interpret because of two major confounding effects: smoking and population dynamics (e.g., worker self selection). The effects of smoking and age on ventilatory function of the general population have been studied in detail (*27*). In studies on welders (*28*), no statistically significant differences between welders who smoked and controls who smoked could be detected: for nonsmoking welders and controls, only closing volume, closing capacity, total lung capacity and N_2-cardiogenic oscillations were significantly different, presumably due to the deposition of welding fume particles in peripheral small airways. Studies of respiratory effects in other populations in the metal industry can show more pronounced effects (*29*), although they may not become apparent until after 30 years exposure or longer (*30*) for some occupations.

The role of population dynamics through worker self selection among the welding population has been demonstrated (*31*). Of 100 welders first examined in 1963, only 19 could be identified and reexamined in 1978 in an effort to determine the effects of 15 years of exposure to welding fumes. For the two cohorts the average values of forced vital capacity (FVC), maximum expiratory flow volume at 50% vital capacity ($MEFV_{50}$) and forced expiratory volume over the first second (FEV_1) were found to be higher in 1978 by approximately 4%, 0.6% and 4%, respectively. This apparent slight increase in the respiratory function of these welders is however due to the fact that while the initial cohort had values of FVC, $MEFV_{50}$ and FEV_1 of approximately 108, 107 and 105% of normal, respectively, those welders with more nearly average respiratory characteristics left the occupation and could not be reexamined. Those welders who remained, however, were the individuals whose respiratory characteristics were the highest, having in 1963 values of FVC, $MEFV_{50}$ and FEV_1 of 115, 119 and 113% of normal, which in fact had been reduced on the average by 4, 13 and 6% after further 15 years exposure, with various differences in degree and statistical significance due to smoking habits. The opportunity to change jobs is a function of the regional economic situation which has strong variations with time and locality. Thus cross-sectional studies which only examine the age distribution e.g. (*28*) may underestimate the real effects of exposure on a constant population, and variations in population dynamics (i.e., job mobility) may be strongly reflected in differences in cross-sectional studies from widely disparate societies.

The literature discussed above demonstrates the existence of statistically significant exposure related incidence of chronic respiratory tract disease in welders also documented elsewhere (*32*, *33*), and hence there appears to be convincing evidence for a finite risk of delayed health effects for the welding occupation in general. On the other hand, a significant fraction of welders is employed in shipyards, and shipyard workers in general exhibit a statistical overincidence of chronic respiratory tract disease (*34*, *35*), including cancer (*35*, *36*). Thus there is a strong possibility that shipyard welders are partially at risk because of bystander effects related to their place of employment but unrelated to welding.

Possible Cancer Risk for Welders

A number of epidemiological surveys of general welding populations have shown statistically significant overincidence of lung or respiratory tract cancer for this occupation (*32*, *33*, *36-39*) the data of five of these studies (*32*, *33*, *37-39*) is reviewed in Table 5. The five studies encompass some 150,000 welders, represent approximately 420,000 man years at risk, and show an accumulated observed incidence of 415 cases with 308 cases expected, assuming an observed/expected (O/E) ratio of unity for unexposed populations. Although there are slightly different approaches taken in each of the studies, the range of O/E incidence ratios lies between 1.0-2.8 (95% confidence limits) (0.85-3.2 within 99% confidence limits), to be compared with an O/E ratio for unexposed but equivalent populations of the order of 0.6-1.0 (95% confidence limits) (uncorrected for smoking) (*40*). Thus there is sufficient evidence to reject the null hypothesis that welding or being a welder does not contribute to occupationally related cancer incidence.

If the statistically significant overincidence of respiratory tract cancer among welders is due to their occupation, is not a bystander effect (*36*) and is not due to some systematic confounding effect such as smoking habit (welders exhibit an overprevalence of smoking by 22%) (*32*) or other lifestyle effect, then it may have its origin partially in the general working place exposure of all welders, and partially in specific, high risk exposures. A general occupational risk might arise from the lung burden of dust [approximately 2 g in older welders (*14*)] which, if it resulted in an increase of the order of five years in "lung age" over chronological age, could account for the observed overincidence in age specific cancer rate. Technology or job specific risk would be associated with processes which produce welding fumes possessing high carcinogenic potency (i.e. "hot spots").

Table 5. Summary of epidemiological studies of welders which demonstrate a statistically significant excess incidence of respiratory tract cancer.

Author	Locality	Reference population[a]	O[b]	E[a,c]	O/E	p[d]	O/E 95%[e]	Study design and population
Milham (*39*)	Wash. state, U.S.	U.S. age-adjusted	67	49	137 (PMR)	0.05	1.2–1.7	White males; deaths from cancer of trachea, bronchus, lung (1951–70); 2000–3000 welders
Menck (*37*)	Los Angeles Co.	LA Co. age-specific	21(d) 27(i)	34	137 (d + i) (SMR)	0.06	1.0–1.8	White males; lung deaths (d) (1968–70) plus 2 yr incidence (i) (1972–73); 15,300 welders
Dec. Suppl. (*32*)	Great Britain	National age-adjusted	246	192	127 (PMR)[f] 151 (SMR) 116 (SMR)[g]	0.01 0.01	1.3–1.8	All males; lung deaths (1968–69); 128,000 welders
Beaumont and Weiss (*33*)	Seattle, Wash.	U.S. age-adjusted	53 40	40 23.7	1.31 (SMR) 1.69 (SMR)	NS 0.01	0.96–1.6 1.1–2.3	White males; respiratory cancer deaths (1950–76); 3200 welders and burners (base rate 38/100,000)
Breslow et al. (*38*)	California	Noncancer patients in same hospitals	14/16[h]	9/16[h]	1.5	0.05	1.1–1.9	Males, lung cancer patients (1949–52); 493 cases; 493 controls matched for smoking habits; 5 yr employment as welders and sheet metal workers doing welding

[a]The number expected for any given cohort is extremely dependent on the reference population chosen and hence the observed/expected ratio will exhibit the same sensitivity.
[b]Observed.
[c]Expected.
[d]Significance.
[e]Limits to O/E within 95% confidence interval.
[f]PMR social class adjusted.
[g]SMR adjusted for smoking [excess incidence = 122% = SMR (expected) 110–160 = 135 smoking adjustment: 151–135 = 116).
[h]Proportion of cases among welders (14 cases, 2 controls).

Individuals who occupationally perform welding fall into several distinct categories. In countries, like Great Britain, with a well defined apprenticeship system, workers enter the welding trade at the age of 17 and remain for the major fraction of their working life (*21*). Approximately one half of this population is itinerant within the trade, being occupied with a wide range of technologies both daily and within a working lifetime. Perhaps an equal number of individuals are engaged in rather well defined and limited range of welding situations, and are exposed over relatively long periods to a narrow range of types of welding fumes (e.g. stainless steel welders). In addition to these fulltime welders there exists a large population of individuals in other jobs who weld occasionally and who contribute of the order of 30% fulltime equivalents to the populations listed in Table 3.

Since the nominal composition of the fumes from most welding processes is known (*1-3*, *10*), it is instructive to examine the technologies most representative for the industry in order to determine if there exist well defined cohorts who might suffer excessive exposure to suspected carcinogens, and conversely, to identify unexposed cohorts who might serve as control groups. If the welding population can be shown to have a sufficiently inhomogeneous exposure to carcinogens, one could then address the problem of identifying, quantifying, and eliminating the "hot spots" thereby defined.

Of the five metals which have been identified or strongly suspected as being human carcinogens (in some frequently unknown form) [As, Be(?), Cd, Ni, Cr] (*41-47*), nickel and chromium appear in significant concentrations only in the fumes from stainless and alloy steels, arsenic is a ubiquitous trace impurity in most welding fluxes, cadmium is absent from welding consumables but occurs in many brazing alloys (an allied but separate trade), and beryllium is most probably present only in certain highly unique situations. Approximately 40% of all MMA welders (on mild steel), mostly those employed in

Table 6. Typical exposures (8 hr).

% of welding population	Process	Exposure, $\mu g/m^3$ Total fume	Fe_2O_4	Benzo (a) pyrene	Total organic (gaseous)	Total Cr	Cr(VI) (water-soluble/ insoluble)	Total Ni	As	Asbestos	Cutting Oil	NO_2	O_3
36 ± 5	MMA/MS unprimed[a]	5000	2000	0.06	15	0.5	0.25/0.25	–	2.5	+[b]	+	+	–
24 ± 5	MMA/MS shop primed surfaces[a]	10000[c]	4000	?	300[c,d]	1.0	0.5/0.5	–	5	+[b]	?	+	
10 ± 5	MMA/MS	5000	500	–	–	200	140/10	50	–	–	+	+	–
2 ± 1	MIG/SS	2500	1250	–	–	250	20/5	125	–	–	+	+	–
3 ± 2	AL/MIG	10000	800	–	–	8	4/4	–	–	–	–	+	+

[a]MIG/MS and MAG/MS values are expected to be similar to corresponding MMA/MS exposure but depend to such a great extent on consumables etc. that MIG/MS and MAG/MS welders cannot be assumed to form a homogeneous exposure group.
[b]Shipbuilding and structural steel trades.
[c]Assuming a zinc-based primer.
[d]Assuming a formation rate of 3 ± 2% of that of total fume.

shipyards, utilize base material coated with shop primer, an antirust compound, usually a polyvinyl butyral or phenolic or epoxy resin, containing iron oxide and/or zinc tetraoxychromate. Welding on this material produces a fume containing 1-3% organic gases from the pyrolytic decomposition of the primer. In addition to aldehydes, alcohols and ketones, this organic "soup" has been shown to contain a vast variety of compounds such as naphthalene, methylbenzofurene, phenol, cresol, dioxane, pyridine, 2,4-dexadienal, 2-hexanone, and benzene and other saturated and unsaturated alphatic and aromatic hydrocarbons (C_6-C_{14}) (*48*, *49*) and therefore must be suspected of posessing some carcinogenic potency of unknown but nonzero magnitude. Most other welding fumes are free of organic material (a notable exception being that from cellulose electrodes used on pipelines).

In addition to welding fumes, bystander exposure to carcinogens might be significant: at least 40% of all welders have some historical contact with asbestos (*21*, *39*), while those working in machine shops have occasional exposure to cutting oil mist, a suspected sinonasal carcinogen (*50*, *51*). Most welders are exposed to iron oxide particulates, which alone are probably inactive, but which appear to be a cocarcinogen for benzo(a)pyrene (*52*) which has been identified in some workshop backgrounds (*3*). The magnitude of possibly carcinogenic exposures which are expected to accompany the use of some representative welding technologies is summarized in Table 6, derived from nominal concentrations and compositions shown in Figure 1 and Table 3, respectively.

Semiquantitative Risk Assessment

The ubiquitous exposure of most welders to possible work place carcinogens as illustrated in Table 6 might well explain the observed excess incidence of respiratory tract cancer summarized in Table 5. The demonstrated 5:1 excess incidence of mesothelioma among dockyard welders in Plymouth, England (*36*), giving an absolute rate of 80/100,000 cases/man year could contribute only of the order of 10% to the average overincidence of welders respiratory tract cancer if this "signal" cancer due to asbestos exposure is included, although no specific mention of this tumor is found in the studies listed in Table 5. Naval dockyards in general, and Plymouth in particular, may represent a mesothelioma "hot spot." On the other hand, it is tempting to try to estimate what fraction of actual risk is represented by the exposure of stainless steel welders to Cr(VI) and Ni since, because of their skills, they represent a coherent cohort with reasonably well defined exposures with a minimum of confounding effects (no asbestos), and the health effects of occupational exposure to Ni and Cr have been studied to a great extent in the respective (nonwelding) Ni and Cr industries (*41-47*).

Although a linear dose-response model is probably inappropriate for human cancer (*53*), and the available and relevant information is fragmentary and frequently inaccurate, one can attempt a survey of exposure-response data found in the literature of epidemiological studies carried out in the chromium and nickel industry. A tentative summary of relevant data is presented in Table 7. Here

Table 7. Approximate carcinogenic dose-response relationship.

	Total metal (cumulative exposure), $mg/m^3 \cdot yr^a$	Absolute lung cancer incidence rate/100,000	Latency, yr (average)	Age group at risk (average)
Chromium industry	Total Cr(VI)			
Cr plating (*54*)	0.5	< 360[b]	(16)	(58)
Ferrochrome (*55*)	0.44	100	5–42 (21)	54–79
Chromate (*56*)	2–25 (4)	600	8–39 (22–32)	45–64
Chrome pigment (*57*)	2.0	760	5–21 (15)	(50)
Chrome pigment (*58*)				
Average Cr(VI)	3 ± 2	500 ± 250	(21)–(15)	45–79
Nickel refining industry	Total Ni			
(Clydach) (*59, 60*)	11–110[c]	64 (lung)	15–40	44–79
Average[c]	33	21 (nasal)	20–34	(68)

[a]Estimated geometrical average.
[b]Maximum consistent with observed nonsignificant overincidence.
[c]Exposure is to $Ni(CO)_4$ + Ni + NiO + Ni_3S_2.

estimated geometrical-average cumulative exposures to Cr(VI) and average lung cancer rates are listed together with the relevant age group and range in latency period for the four industries: chromium plating and ferrochrome, chromate and chrome pigment production (*54-60*). Exposure in the case of chromium plating is principally to water-soluble Cr(VI), while in the other three industries it is to a varying mixture of Cr(VI) and Cr(III) of different solubilities. The values shown must be considered highly uncertain and the tentative conclusion that these industrial exposures can be considered to result in an approximately similar risk per dose in the range shown must be considered extremely speculative, since an additive model of carcinogenicity with a single causitive agent is implicitly used. Note that if the distributions of exposure shown in Figure 1 are typical in other industries, there is approximately a range of a factor of 16 for the exposure levels of 90% of the cohorts studied.

Historical exposures are extremely difficult to estimate since even in those cases where reliable concentration measurements have been made, they show such a wide interindividual range that one can question the statistical use of a geometrical (or any other) average: compositions can frequently only be arrived at by an educated guess, leading to an order of magnitude uncertainty in estimates for total exposures. Furthermore, for the case of Ni and Cr, the actual causative agents are unknown and there is emerging evidence that at least for Ni, there is an extremely wide variation of carcinogenic potency for different substances.

In spite of the obvious speculative nature of the data of Table 7 one could attempt to use the dose-incidence data to predict order of magnitude effects for stainless steel welders. A 20-year exposure to the average Cr(VI) concentration of 0.15 mg/m^3 found for MMA/SS welders would give an average total Cr(VI) exposure of 3(mg/m^3) (years), similar to that found in Table 7 in the chromium industry, and hence might be expected to lead to the same magnitude of cancer incidence. Obviously the exposure, and hence on this simple model the expected incidence rates, for MIG/SS welders are of the order of a factor of six lower than for MMA/ SS welders. The risk for Ni for these trades, although non-zero, is negligible compared to that for Cr(VI), with the exception of the relatively few MIG welders using pure Ni filler wire. Such interindustrial comparisons, if appropriate, can also be used as an aid in the proper design of epidemiological studies by indicating those exposure levels, latency periods, and cohort sizes consistent with detection of an effect at an acceptable level of significance. For example, a cohort of some 200 MMA/SS welders exposed at high total fume concentrations (10 mg/m^3) for the period 1950-1955 and followed to 1980 should provide statistical material just sufficient to verify or reject the model presented above.

One unavoidable conclusion to be made based on the preceeding discussion is that unless water soluble Cr(VI) is not a carcinogen of potency comparable to that of other industrial Cr(VI) exposures, the manual metal arc welding of stainless steel with conventional electrodes represents a "hot spot" for risk of occupationally related respiratory tract cancer. Should this exposure represent a potential

overincidence of a factor of three (SMR = 300), then the 10% subcohort of MMA/SS welders could contribute to approximately a 30% overincidence for the entire industry (SMR = 130). It is not clear in which direction systematic errors and bias in the selection of data will effect such a zeroth order risk assessment. Certainly the probable nonlinearity of the dose-incidence relationship will provide for a disproportionately large effect among those individuals with significantly higher than average exposures.

Since there is as yet little epidemiological data (on selected subcohorts of welders with restricted exposures) on which to attempt an evaluation of the type of risk assessment proposed above, justification for the supposition of process-dependent "hot spots" (especially of genetic risk) must be sought on the basis of indirect (i.e., nonhuman) experiments on the (geno)toxic properties of welding fumes.

Screening Tests for Mutagenesis and Carcinogenesis

Utility of Screening Tests

Because of the existence of an extraordinarily wide variety of welding atmospheres, a direct determination of toxic risk for welding fume by traditional *in vivo* methods is impractical: such studies would only provide information concerning a single process or group of processes and only with difficulty could be extrapolated to a larger segment of the industry. Similarly evaluation of most single processes by means of human epidemiology is impractical. On the other hand, short-term screening tests for mutagenesis and carcinogenesis would appear to be ideally suited for use in evaluating the relative genetic risk entailed by exposure to various welding fumes assuming that the obvious problems concerning exposure-related dose for such complex aerosol systems can be resolved. The fumes have an aerodynamic mass median diameter (MMD) of the order of 0.2 μm (*61*) (MMA fumes have an additional component with MMD = 1 μm) and a demonstrated elemental deposition in the human respiratory tract of the order of 30-40% (*62*).

Despite the uncertainty in the relationship between mutagenicity and carcinogenicity of metals (*41*, *42*, *47*, *63-66*), semiquantitative fast *in vitro* screening methods could be used to assess relative risks of welding fumes of similar composition by studying the origin of variations of genotoxicity and hence by implication their possible carcinogenic potency (*67-69*). Such conclusions can be based on the expectation that a number of steps which determine specific (i.e., molar) genotoxicity *in vitro* (solubility, species formation rate and activity of intermediate metalorganic metabolites, membrane diffusion, the nature and efficiency of detoxification pathways and repair mechanisms, and particle cell interactions (such as phagocytosis)) can be expected to exist *in vivo* as well (*70-75*).

Although at present there is not sufficient information to be able to interpret the significance of the general observation of mutagenicity of a large number of the metals many of which can be found to some degree in various welding fumes, there would appear to be strong incentive to examine the possibility for the *in vitro* risk assessment of nickel and chromium, not only because of their importance in welding, but because of the widespread worker exposure in other industries. The development of specific screening techniques for Ni and Cr welding aerosols, and the subsequent demonstration of their general applicability would be a significant step in industrial hygiene.

Mutagenicity of Ni and Cr

The present state of understanding of the mutagenicity of Ni and Cr has recently been reviewed (*42*, *47*, *66*, *76*). Nickel induces base-pairing aberrations of nuclear acids, infidelity of DNA replication, chromosome aberrations in cultured mammalian cells, sister chromatid exchange in cultured human lymphocytes *in vitro* and aberrant DNA synthesis and/or repair and binding to nuclear macromolecules *in vivo*. Neoplastic cell transformation can be induced by particulates of crystalline Ni_3S_2 (a potent experimental animal carcinogen) which excite phagocytosis but not by amorphous NiS (a concarcinogen).

Hexavalent chromium, Cr(VI), induces infidelity of DNA replication, is mutagenic in bacterial test systems (*B. subtillis*, *S. typhimurium*), and induces chromosomal aberrations and aberrant DNA synthesis or repair in tissue culture cells *in vitro*. The cytotoxic activity of Cr(VI) is eliminated by the extracellular reduction to Cr(III), an oxidation state for which there is little membrane permeability. On the other hand Cr(III) is highly effective in inducing infidelity of DNA synthesis, indicating that Cr(III) may be the ultimate carcinogen and that reduction of Cr(VI) at a target molecule may be the critical carcinogenic step (*77*). Only $CaCrO_4$ has been established as an experimental animal carcinogen, and there is considerable uncertainty about the exact role played by solubility of Cr(VI) compounds in the determination of their carcinogenic potency (*42*, *43*, *47*).

Table 8. Range of distribution in oxidation state and solubility fraction for Cr and Ni in stainless steel welding fumes.

Process and oxidation state	Water-soluble, %	Serum-soluble, %		Insoluble, %	Total, %
		pH = 8.8	pH = 7.0		
MMA SS					
Cr(III) + Cr	0			0.2–2.1	0.2–2.1
Cr(VI)	2.2–4.3			0.03–0.42	2.2–4.3
Total Cr	2.2–4.3			0.2–2.5	2.4–6.4
Ni	0.01–0.3			0.27–1.6	0.38–1.9
MIG SS					
Cr(III) + Cr	0			3.56–13.78	3.56–13.78
Cr(VI)	0.005–1.5[a]			0.01–0.42	0.02–2.0
Total Cr	0.005–1.5			3.60–13.8	4.06–15.3
Ni	0.05–0.25			3.5–6.3	3.5–6.5
MIG Ni[b]					
Ni					
Ni:NiO = 1:1	0.2–0.4	0.5–1.2	13–43		69–72
Ni:NiO = 1:10	0.2–0.35	0.5–0.6	7–9		56.3–68.3

[a]Decays rapidly (is reduced to 0.5% after 24 hr at room temperature) (*78*, *79*).
[b]Data of Nieburh et al. (*80*).

Mutagenicity Studies of Welding Fumes

A number of pilot studies have recently been undertaken to determine the extent and origin of genotoxicity of welding fumes. Such a study is necessary in any attempt to rank fumes from various processes in terms of relative genetic risk. The need for rapid screening methods can be inferred from Table 8, which shows the range of Cr and Ni in various solubilities and oxidation states in some typical MIG/SS and MMA/SS welding fumes. It can be seen that relative concentrations of individual components vary by an order of magnitude even in the limited sample shown here, and presumably some rapid method must be developed to determine the risk associated with each of the various combinations of metals produced.

Stainless steel welding fumes are positive in the Salmonella histidine revertant plate incorporation test (*81*, *82*), where the active mutagen has now been shown to be Cr(VI) (*83*, *84*). Fumes from MIG/SS show a specific (molar) revertant rate equal to that for their water soluble Cr(VI) content while those from MMA/SS show a reduced rate indicative of an antisynergistic effect. The addition of microsomes results in a (occasionally complete) reduction of the effect. The test system is negative for fumes which contain only Ni, and for others in which Cr(VI) is absent (including those from mild steel welding processes).

A slight but statistically significant increase in mutagenicity is observed for stainless steel welding fumes in the *N*-thioguanine resistence of V79 chinese hamster cells which survive exposure to the highly toxic material (*82*).

The recessive lethal test in drosophila is negative for exposure in the larval stage to MIG/Ni fumes (a mixture of Ni:NiO) and to MIG/SS particles, and to fresh MIG/SS fume in the adult stage. No significant enhancement for adult sensitivity to DES was found to result from fresh MIG/SS exposure (*85*).

Aqueous solutions of $NiSO_4$ and aqueous and (fetal calf) serum-soluble fractions prepared from a Ni rich welding fume (MIG/Ni) demonstrate equal specific activity in inducing sister chromatid exchange in human peripheral lymphocytes in culture. The serum solubility of both Ni and NiO is extremely high at physiological pH (7.2), as shown in Table 8 (*80*).

Water-soluble Cr(VI) and fumes from an MMA/SS welding process representing an equivalent Cr(VI) dose show similar transplacental genotoxic potency in interperitoneal administration in the mouse spot test (Fleckentest) (*85*, *86*). Stainless steel fume particles are cytotoxic and genotoxic in cultured mammalian cells (*87*, *88*).

From these pilot studies it can be seen that Cr(VI) and Ni as contained in welding fumes apparently exhibit the same types of genotoxicity as is expected for these metals in general (*60*, *73*, *89*, *90*). Since there is no evidence to the contrary, one should assume that the actual risk for genetic damage and other delayed health effects to welders can be expected to be similar to that found in other industries with exposure to these substances. The presence of some unique combinations, such as ozone-Cr(VI), Ni-Mn, however, might result in local

synergistic or antisynergistic effects, which should be studied in detail.

Summary and Conclusions

Throughout the industrialized world the welding industry is found to provide a relatively large population with a potential exposure to high concentrations of a wide range of toxic and biologically active material, occupational exposure to some of which, albeit in other forms and in other industries, is suspected of inducing human respiratory tract cancer. *In vitro* and *in vivo* studies of some representative welding fumes demonstrate mutagenic, embryotoxic, cytotoxic and genotoxic potential. Epidemiological studies show that welders exhibit a statistically significant excess incidence of respiratory tract disease, including cancer, which appears to depend on cumulative exposure. Further evidence implies that specific occupational risk, especially of delayed health effects, may be extremely process-dependent. There is also strong evidence that the local workshop environment significantly influences the degree of such risk. The factors which can effect the absolute health risks experienced by different welding cohorts should in principle be controllable if they can be identified. A demonstration that inhomogeneous risks are primarily restricted to "hot spots" would have major implications for the assignment of priorities for the use of limited resources for risk reduction within the industry.

The first indication of a significantly enhanced lung cancer risk (i.e., a "hot spot") for a cohort of stainless steel welders which satisfies the necessary criteria of length and magnitude of exposure, and latency period has recently been published (*91*). For the cohort studied (234), mostly MMA/SS welders with a minimum of 5 years experience: average exposure of 16 years (3735 man-years) to Cr(VI) concentrations of approximately 216 $\mu g/m^3$) three cases of respiratory tract cancer were found vs. 0.68 expected. The average cumulative exposures of 3.4 (mg/m^3 years) result in a risk rate of 82/100,000 cases/man-year with a local background of 18/100,000: a risk ratio of 4.4:1. These observations lie within a factor or two for the risk ratio and within a factor of six for the absolute excess incidence rate predicted for this exposure to Cr(VI) by the crude semiquantitative risk assessment model presented. Although it is obvious that there is not as yet sufficient evidence on which to test any health risk model for welders, it is clear that the combination of risk assessment methodologies and good epidemiological data will be a powerful tool for the future.

The international welding industry would appear capable of providing a large number of model populations on which to base the development of techniques of multifocal epidemiological studies to determine the origin and extent of process-specific risk. Great care must, however, be taken in design of the study protocols to cope with the observed differences between various welding populations. Recent discussions concerning the variation in age adjusted lung cancer incidence with occupation found for local populations (*55*), and the strong urban-rural gradient (*92*) which they exhibit, point to a possible uncertainty in expected incidence rates of a factor of from two to four: the results of multifocal epidemiological studies carried out on essentially similarly exposed populations would be extremely useful in helping to establish guidelines for the choice of appropriate reference populations, without which it may be extremely difficult to prove the existence of occupationally related excess cancer risks. The parallel development of *in vitro* fast screening tests for mutagenesis and/or carcinogenesis appropriate for use with metallic particulate aerosols might provide a unique opportunity for the establishment of practical risk assessment protocols for use in the metal industry in general. The resulting protection against exposure to carcinogens should reduce the risk for genetic effects in general (*93*).

Without the development of risk assessment methodologies, protective legislation (i.e., TLVs) based on the concept of homogeneous risk, if set at the lowest feasible level, will penalize industries with low risk exposures, while elevated compromise levels might permit dangerous exposures to unidentified high risk material. Finally, it should be pointed out that the wealth of technologies available to this important, populous industry ensures that if "hot spots" of risk can be identified, the means of reducing risk at the source are at hand, provided appropriate alternate low risk procedures can be identified.

Added in proof: Analysis of the citations of a recent literature search (*2*) has uncovered over 100 cases of welders who exhibit abnormal epithelial proliferation ("fibrosis"). For the more than 70 cases for which welding history is known and diagnosis is verified by pathology, the observed incidence is uniformly distributed over starting age (13-52 years) and length of exposure (3-40 years), and does not appear to indicate any specific process-dependent risk (e.g., stainless steel welders account for 5-10% of the welding population), although *in vitro* studies show that fumes from stainless steel welding have a high fibrogenic potential compared to those from other processes (*94*).

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Erratum

C. Jelinek (Food and Drug Administration)
Environmental Health Perspectives 39:143-151
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The author has discovered that two data entries in the table on p. 147 are incorrect. Under the column headed "Current", the value "0.25" should be "0.025", and the value "0.15[b]" should be "0.015[b]".

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Assessment of the Health Effects of Atmospheric Sulfur Oxides and Particulate Matter: Evidence from Observational Studies

by James H. Ware,* Lawrence A. Thibodeau,* Frank E. Speizer,*,† Steven Colome* and Benjamin G. Ferris, Jr.*

Steadily rising energy costs have increased the need for reliable information on the health effects of atmospheric sulfur oxides and particulate matter. Because ethical and practical considerations limit studies of this question under controlled conditions, observational studies provide an important part of the relevant information. This paper examines the currently available epidemiologic evidence from population studies of the health effects of these pollutants.

Nonexperimental studies also have important limitations, including the inability to measure accurately the exposure burden of free living individuals, and the potential for serious confounding by other factors affecting health. We begin with a discussion of some of these methodologic issues. The evidence is then reviewed, first in association with fluctuations in 24 hr mean concentration of sulfur oxides and particulate matter, and then in association with differences in mean annual concentration. In the last section, this evidence is summarized and used to approximate the exposure-response relationship linking pollutant concentrations with mortality and morbidity levels.

Introduction

In view of the potential for adverse health effects of air pollution, and the expense of control measures, reliable assessment of the health effects of different air pollutants is an important public health problem. Lowrance (*1*) has defined four tasks in this assessment: identifying the health effects; quantifying these effects at various ambient concentrations; estimating how many people are exposed at these levels; and calculating the overall health risk associated with a given degree of air quality. This paper addresses the quantification of the health effects of sulfur oxides and particulate matter, especially at ambient concentrations near the present air quality standards.

The health effects of these air pollutants can be studied to some extent in controlled conditions. Laboratory studies of animals allow careful control of the concentration of individual pollutants and conditions of exposure, as well as detailed study of the effects on study animals. These studies have been useful for identifying possible mechanisms of action and potential health effects. However, it is

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difficult to use animal studies to quantify these effects in human populations, primarily because the basis for extrapolating from animal to man is uncertain. The uncertainty of such extrapolation is increased by significant interspecies variability in the response to pollutants.

Laboratory studies with human subjects avoid extrapolation from animal to man but raise other concerns, such as ethical considerations and practical difficulties in studying long-term exposures. In addition, laboratory studies cannot duplicate the activity patterns and pollutant mixture experienced by free living populations. Within these constraints, studies involving human subjects can be used to establish the response to short-term exposure.

Studies of occupational groups have been suggested as another source of information. Although these studies may provide good estimates of exposure, the mix of pollutants and concentrations is usually different from ambient air. Exposures are for 8 hr or less rather than on a more continuous basis. Temperature and humidity conditions are also likely to differ from those experienced by the general population. Furthermore, the working population differs from the general population in important ways. The very young, elderly and ill persons are not included. There is considerable selection by the employer and self-selection by the worker, so that those with current disease or who are more sensitive or susceptible are not as well represented as in the general population. As a result, one cannot conclude from a negative study in an occupational group that the same exposure is safe for the general population. If an association between an air pollutant and a health effect is found in an occupational setting, there may be a greater association in general populations.

Because of the limitations of each of these types of investigation, epidemiologic studies in general population groups provide much of the relevant information about the health effects of sulfur oxides and particulate matter at levels of exposure near present ambient standards. Here, too, there are limitations with respect to estimating exposure and measuring effects. Other risk factors, such as cigarette smoking and occupational exposures, must be considered, and confounding factors, such as socioeconomic status, race and weather must also be evaluated. In these studies, exposures are not subject to manipulation, though ambient levels can change during the course of a study. This makes it difficult to determine whether mean concentration, peak concentration, variability, or some other aspect of air pollution concentration is the most important determinant of health effects. Observational studies cannot demonstrate cause and effect, rather we infer causality based on the precepts proposed by the Surgeon General's Advisory Committee on Smoking and Health (*2*) and by Hill (*3*): the strength of the association, the consistency of the data, the specificity of the results, the temporality of the observations, the demonstration of a biological gradient and the plausibility and coherence of the results. Ideally, findings will be replicable by specific experimentation, and conclusions will be further strengthened when different approaches or methods yield similar results.

The next section of this paper briefly summarizes the methodological issues which should be considered in evaluating nonexperimental studies of the effects on health of exposure to atmospheric sulfur oxides and particulate matter. We then review the evidence from selected studies of the association between mortality and morbidity levels and 24-hr mean concentration of sulfur oxides and particulate matter the evidence linking mortality and morbidity levels to annual mean concentrations. The evidence is summarized in the final section.

Methodological Issues in Observational Studies

Observational (nonexperimental) studies of the association between health and air pollution are sometimes viewed as natural experiments in which the exposure to pollutants varies over groups or time. However, this view ignores several special characteristics of observational studies of air pollution. One of the most important is inaccurate measurement of the exposure burden of individuals. Pollution data are usually obtained from one or several outdoor monitoring stations, but the exposure burden can vary greatly between individuals living in the same neighborhood because of special features of the outdoor micrometeorology and the indoor environment (*4-6*). The effects of errors in the independent variable on the estimated associations between air pollution and health effects depends on both the size and expectation of the errors. Many health endpoints, including lung function, hospital admission and frequency of symptoms, also are measured with substantial variability. When an association between air pollution and health is found, collinearity (high correlation) of sulfur oxide and particulate concentrations (*7*) and the possibility of complex chemical interactions reported from laboratory studies (*8, 9*) frequently make it difficult to associate the effect with either pollutant alone (*10*).

Observational studies of respiratory disease or

lung function must consider a host of confounding variables (*11*), many of which have greater health effects than air pollution. When these variables are ignored or inadequately measured, resulting bias can easily be greater than the association of interest. In addition, many observational studies use linear or other simple models to summarize complex data sets without assessing the adequacy of the model. Unless data displays, simple groupings or other analyses are used to show that these models are properly summarizing the data, one can only have limited confidence in the results.

These factors, taken together, create additional uncertainty in interpreting observational studies in comparison with laboratory experiments. The most difficult problem in interpreting the evidence from a group of observational studies is determining how effectively these potential problems have been addressed in each study.

There is an unavoidable element of subjectivity in the assessment of evidence. In an effort to reduce that subjectivity we have included in the assessment those studies which satisfy five criteria.

(1) They have been reported in the open literature.

(2) Concentrations of both sulfur dioxide and particulate matter were reported.

(3) Major confounding factors were controlled, particularly temperature in studies of acute exposure, and smoking, race and socioeconomic status in studies of chronic exposure.

(4) The findings pertain to concentrations less than 1000 $\mu m/m^3$ for both sulfur dioxide and particulate matter.

(5) The data collection, analysis and interpretation were free of error or potential bias which could be reasonably expected to substantially affect the results.

Studies failing to meet one or more of these criteria were also included when discussion of their validity and significance was seen as an important part of assessing the evidence from observational studies.

Health Effects of Acute Exposure to Sulfur Oxides and Particulates

The earliest studies of the acute health effects of air pollution focused on dramatic episodes of severe air pollution (*12-18*). The sudden increases in mortality and morbidity that accompanied these episodes and the frequency and severity of respiratory complaints left little doubt that air pollution was, at least in part, the cause of the adverse health effects. Investigators also recognized that weather, particularly extreme temperatures, could influence mortality and morbidity rates.

A substantial reduction in ambient sulfur oxide and particulate concentrations, achieved in most English and American cities by the 1970's, produced a gradual decline in severity and eventual disappearance of episodes in which either sulfur dioxide or particulate matter exceeded 1000 $\mu g/m^3$ (measuring particulate matter either by the British Black Smoke method or as Total Suspended Particulates). Episode studies were gradually supplanted by studies of fluctuations in daily mortality over extended periods, and investigations of potentially more sensitive indices of health effects, including lung function and respiratory disorders. Sensitive population subgroups, such as asthmatics and children, have also been studied. The pollution concentrations in studies of acute exposure have typically been measured by 24-hr mean concentrations, though high level exposures for shorter periods might be important.

Counts of total daily mortality show a seasonal pattern with a peak in winter, and rates on successive days are interdependent. Early studies used the deviation of daily mortality from the 15-day moving average to eliminate seasonal effects. More recently, investigators have used sophisticated time-series-analysis techniques in an effort to eliminate seasonal effects and other long-term trends affecting daily mortality. Elimination of seasonal effects by these methods may be incomplete, and this becomes especially important when investigators attempt to identify pollution effects that are small relative to effects of temperature, season and even day of the week. We will return to this issue in the discussion of individual studies.

Morbidity data are more difficult to gather than daily mortality figures. For that reason, investigations of morbidity effects of acute exposure to sulfur oxides and particulate matter have usually been small, permitting relatively simple analysis. These studies would be unlikely to detect small increases in morbidity at relatively low air pollution concentrations.

Studies reported in this section used three separate measures of particulate pollution. The British studies used the British Black Smoke method and reported particulate levels in $\mu g/m^3$ (BS). Some American studies used the filter soiling method and reported particulate concentrations in units of Coefficient of Haze (CoHs). Other American studies measured Total Suspended Particulates (TSP) by the high-volume sampler method. Results are reported for each study in the original units, and the relationship between the different measures is considered when summarizing the evidence.

Mortality Effects of Acute Exposure to Sulfur Oxides and Particulate Matter

In this section, we examine studies of the association between daily mortality rate, as measured by the recorded number of deaths, and 24-hr average concentration of sulfur dioxide and particulate matter. The clearest evidence comes from studies of relatively high pollution concentrations, while studies of lower concentrations have been equivocal, primarily because collinearity of temperature and other weather variables with pollution concentrations have made it difficult to interpret associations between daily mortality and air pollutant concentrations.

Studies of Daily Mortality in London. Two important British studies bearing on mortality effects of acute exposure to SO_2 and particulate matter at concentrations near present 24-hr air quality standards were reported by Martin and Bradley (*19*) and Martin (*20*). Martin and Bradley related daily mortality from all causes (and from bronchitis and pneumonia) to the concentrations of SO_2 and black smoke (BS) in London during the winter of 1958-59. The authors found a considerable number of coincident peaks in pollution concentration and daily mortality. The correlation of mortality from all causes with air pollutant concentration, measured on the log scale, was 0.61 for BS and 0.52 for SO_2. The correlation between mortality and mean daily temperature was –0.03 (not significant), while the correlation of mortality with humidity was 0.19 (significant at the 0.05 level). The authors noted that about two-thirds of the air pollution episodes were accompanied by thick fog, and the correlation between mortality and visibility was found to be –0.55. Visibility is influenced both by fog and particulate pollution.

Although the authors emphasized the relationship between differences in pollution concentration and differences in death rate on successive days, their paper provided total deaths, smoke concentration and SO_2 concentration from November 1, 1958 to February 28, 1959. We have re-examined their data after excluding the month of February, as an epidemic of Type A influenza had a significant influence on daily mortality in that month.

For the remaining 92 days, the deviation of each day's total mortality from the 15-day moving average (truncated at each end of the series) was computed. The average deviation is given for intervals of BS concentration in Table 1 and SO_2 concentration in Table 2.

Although Lawther (*21*) has suggested that the number of deaths increased significantly when BS rose above 750 $\mu g/m^3$ and SO_2 concentrations exceeded 710 $\mu g/m^3$, these tables do not suggest those values. If one begins with a threshold hypothesis, that mortality is not affected until air pollution concentrations exceed threshold levels, one might choose threshold values of 500 $\mu g/m^3$ of BS and 300 $\mu g/m^3$ of SO_2 from these data. However, the data are also consistent with a monotonic exposure-response hypothesis, that mortality level increases with air pollution concentration over a broad range of values, including those just cited.

A similar analysis was carried out by Martin for the winter of 1959-60 (*20*). That winter had fewer incidents of high pollution. The significant positive correlation between mortality and pollution was still present, although the author reported that the correlation coefficients were somewhat lower than in the previous year. Tables 3 and 4 show Martin's results combining high pollution days from 1958-59 and 1959-60, excluding days with pollution concentrations lower than the previous day. The mean deviation is positive in every group reported. Bronchitis mortality was also found to be significantly, though less strongly, correlated with pollution level. Pneumonia mortality was not found to be correlated with pollution.

Table 1. Average deviation of daily mortality from 15-day moving average, by concentration of smoke (London, Nov. 1, 1958, to Jan. 31, 1959).[a]

Smoke concentration, $\mu g/m^3$ (BS)	Number of days	Mean deviation
100–199	6	–20.82
200–299	12	–13.65
300–399	18	–10.80
400–499	19	–7.15
500–599	9	10.89
600–699	6	19.72
700–799	7	4.17
800–1199	10	21.49
1200+	5	38.36

[a]Data of Martin and Bradley (*19*).

Table 2. Average deviation of daily mortality from 15-day moving average, by concentration of SO_2 (London, Nov. 1, 1958, to Jan. 31, 1959).[a]

Smoke concentration, $\mu g/m^3$	Number of days	Mean deviation
100–199	17	–13.01
200–299	29	–12.16
300–399	22	6.87
400–499	11	9.32
500+	13	27.21

[a]Data of Martin and Bradley (*19*).

Table 3. Average deviation of daily mortality from 15-day moving average, by concentration of smoke (BS) (London, 1958-60).[a]

Smoke concentration, $\mu g/m^3$ (BS)	Number of days	Mean deviation
500–599	9	5.2
600–699	6	13.0
700–799	9	9.2
800–1099	8	15.6
1100+	7	40.0

[a]Data of Martin (20).

Table 4. Average deviation of daily mortality from 15-day moving average, by concentration of SO_2 (London, 1958-60).[a]

SO_2 concentration, $\mu g/m^3$	Number of days	Mean deviation
400–499	9	9.0
500–599	6	11.6
600–799	9	16.0
800–899	6	19.2
900+	5	39.6

[a]Data of Martin (20).

These two studies represent an important part of the evidence for mortality effects of short-term elevations in SO_2 and particulate pollution. Although temperature was not an important confounding factor in the two winters studied, fog was an important factor in many air pollution episodes, especially in the winter of 1958-59. Reported analyses have not adequately controlled for the effects of fog on mortality. During this period, daily mean concentrations of SO_2 and BS were highly correlated ($r = 0.89$ for the winter of 1958-59). Consequently, these associations cannot be attributed to either pollutant individually.

Additional evidence for acute effects of short-term elevations in sulfur dioxide and particulate matter concentrations was provided by the analysis of a pollution episode in London in December, 1975 (22, 23). Maximum 24-hr concentrations of 994 $\mu g/m^3$ (SO_2) and 546 $\mu g/m^3$ (BS) were reported, and an increase of 100 to 200 deaths above expected totals was observed during the week in which the episode occurred. A doctors' strike in the period immediately prior to this episode had an unknown impact on the mortality data.

Studies of Daily Mortality in New York City. The other principal source of information on variation in daily mortality comes from a series of studies in New York City. This information includes reports (24-26) of several air pollution episodes not discussed here, since pollutant concentrations were too high to contribute significantly to our assessment. However, Glasser and Greenburg (27) carried out an analysis of daily mortality in New York City during the five-year period 1960-64, using only data from the months October through March. The 24-hr average pollution concentrations were based on hourly SO_2 and bihourly smoke shade (CoHs) readings from a single monitoring station. Death rates were analyzed both as deviations from a 15-day moving average and as deviations from the five-year average for that day. The two analyses were said to have qualitatively similar results. In cross-tabulation of daily mortality by SO_2 and smoke shade level, SO_2 appeared to be more strongly related to mortality and was used as an index of pollution in some analyses. Multiple regression analysis showed a stronger association of mortality with SO_2 than with either temperature or rainfall.

Tables 5 and 6 summarize the analysis by Glasser and Greenburg. These results have been interpreted as showing a mortality effect for smoke shade above 5 CoHs and SO_2 above 786 $\mu g/m^3$, though they are again supportive of a monotonic exposure response relationship. Although the observations of daily mortality are correlated, Glasser and Greenburg computed standard errors for the mean deviations by assuming independence. Most

Table 5. Average deviation of daily mortality from normal, by level of smoke shade (CoHs) (New York, 1960-64, October through March).[a]

Smoke shade level (CoH)	Number of days	Mean deviation (SE)
<1.0	26	-2.8 (3.5)
1.0–1.9	160	-1.6 (1.4)
2.0–2.9	318	-2.4 (1.0)
3.0–3.9	239	1.5 (1.2)
4.0–4.9	88	2.5 (2.3)
5.0–5.9	19	18.8 (4.3)
6.0+	9	17.2 (7.8)

[a]Data of Glasser and Greenberg (27).

Table 6. Average deviation of daily mortality from normal, by level of SO_2 (New York, 1960-64, October through March).[a]

SO_2 concentration, $\mu g/m^3$	Number of days	Mean deviation (SE)
<262	112	-3.5 (1.6)
262–524	311	-3.1 (1.0)
525–786	172	1.8 (1.4)
787–1048	66	9.4 (2.0)
>1048	80	11.9 (2.5)

[a]Data of Glasser and Greenberg (27).

of these standard errors were near 2.0, though the entry 18.8 in Table 5 had a quoted standard error of 4.3. The authors also stratified days by temperature into three groups: those more than five degrees below normal, within five degrees of normal, and more than five degrees above normal. The result of the stratified analysis differed little from the unadjusted analysis. However, this simplified approach to covariance adjustment may not eliminate the confounding effects due to temperature. Multivariate analyses of the New York data described below suggest that more careful control for temperature and other meteorologic factors has a substantial effect on the results.

To analyze possible mortality effects of even lower levels of pollution, the 15-day moving average method is not sufficiently sensitive. Furthermore, some authors have argued that more sophisticated adjustment techniques are necessary to ensure that seasonal and temperature effects are eliminated in the adjusted analysis. To achieve that objective, Schimmel and coworkers (*28-30*) have reported three analyses of mortality data from New York City in which the adjustment methodology was refined over time. Buechley et al. (*31*) and Buechley (*32*) have also analyzed some of the same data.

Schimmel and Murawski (*29*) emphasized the common seasonal trends in mortality, pollution and temperature in New York City, and the possibility that nonlinear relationships would make linear regression unsatisfactory as an adjustment technique. They eliminated periods associated with heat waves and analyzed the remaining data in three time periods, 1963-66, 1967-69 and 1970-72. While smoke shade level varied little over the three periods, the average SO_2 level declined dramatically, as shown in Table 7.

Schimmel and Murawski estimated the percentage of premature deaths due to air pollution to be 2.78, 2.48 and 3.20, based on regression analysis of the three periods using a model with no lag effects. The percentage attributed to SO_2 was 0.58, 1.22 and 0.62, values not significantly different from zero. Since the percentage of excess deaths attributed to air pollution differed little in periods with three-fold differences in SO_2 concentration, they concluded that SO_2 concentration is merely an index variable for other unmeasured extraneous variables and not a cause of adverse health effects at these levels.

Schimmel (*30*) continued his analysis of these data by utilizing time series techniques to eliminate any seasonal or other cyclical effects contributing to associations between pollution and mortality. In this analysis, the regression of mortality on SO_2 was not significant and negative coefficients were obtained in some regressions.

Buechley (*31*, *32*) also sought to identify major nonpollutant variables influencing daily mortality and found that mortality was affected by the annual cycle, summer heat waves, influenza epidemics and a temperature variable. These four variables explained 78% of the variation in daily mortality during the 11-year period 1962-72 in New York City. Although SO_2 concentration and particulate level also entered significantly into the regression equation, Buechley found that the coefficient for SO_2 concentration in regression analysis of daily mortality during the winter of 1971-72 was slightly higher than the corresponding coefficient for the winter of 1967-68, even though the mean SO_2 concentration in the second winter was only 10% of that in the earlier period.

Both Schimmel (*30*) and Buechley (*32*) concluded that the associations they found between mortality and air pollution could be explained by joint association with temperature and other weather variables. Their work highlights the limitations of observational studies when the study objective is accurate estimation of small primary relationships when other independent variables are more strongly associated with mortality. These other variables influence the estimate of the primary relationship, and the proper method of adjustment is unknown. Thus, it will be difficult to reliably quantify small mortality effects of fluctuations in ambient pollution concentrations by analyzing observational data.

Table 7. Average pollution levels during three time periods analyzed by Schimmel and Murawski.[a]

Time period	SO_2 level, $\mu g/m^3$	CoHs level
1963–66	112	2.07
1967–69	359	2.27
1970–72	155	2.13

[a]Data of Schimmel and Murawski (*29*).

Morbidity Effects of Acute Exposure to Sulfur Oxides and Particulate Matter

Levels of air pollution which acutely affect mortality rates should affect other health indices, including incidence and prevalence of respiratory disease as measured by emergency room visits or hospital admissions, prevalence and severity of respiratory symptoms as measured by question-

naire during regular contact with a panel of participants, or changes in various aspects of lung function. Unlike mortality rates, these health data must often be specially obtained by the investigator. This has limited the size of morbidity studies. Many studies have used the diary or panel method, in which a group of participants regularly record or report symptoms. Substantial nonparticipation rates have been a problem in many of these studies, and make it difficult to interpret the symptom reports by those from whom observations are obtained.

Illness data were obtained in many of the early severe pollution episodes (*13*, *15*, *33*). This information did little more than confirm the mortality results, though there was some evidence that the increase in illness was not as large in percentage terms as the increase in deaths, and the effects were not so sudden. Martin (*20*) examined hospital admissions for the winters of 1958-59 and 1959-60 and found, after adjustment for day of the week and correction for 15-day moving average, significant correlations for both cardiovascular and respiratory conditions with BS and sulfur dioxide. The average deviations by pollution concentration, given in Tables 8 and 9, show more irregularity than the mortality data.

Table 8. Average deviation of respiratory and cardiac morbidity from 15-day moving average, by smoke concentration (BS) (London, 1958-60).[a]

Smoke concentration, $\mu g/m^3$ (BS)	Number of days	Mean deviation
500–599	9	3.2
600–699	6	–0.7
700–799	9	2.4
800–1099	8	4.9
1100+	7	12.9

[a]Data of Martin (*20*).

Table 9. Average deviation of respiratory and cardiac morbidity from 15-day moving average, by SO_2 concentration (London, 1958-60).[a]

SO_2 concentration, $\mu g/m^3$	Number of days	Mean deviation
400–499	9	2.2
500–599	6	5.1
600–799	9	6.9
800–899	6	12.8
900+	5	12.8

[a]Data of Martin (*20*).

In a second important British study, Lawther et al. (*34*, *35*) collected daily self-reported health status from 194 persons with chronic respiratory disease during the winters of 1959-60 and 1964-65. Health status was reported relative to the previous day, and worsening of health status by self-evaluation was clearly associated with increases in air pollution. The authors reported that this effect could be seen on days when the 24-hr average level of SO_2 exceeded 500 $\mu g/m^3$ and smoke exceeded 250 $\mu g/m^3$ (BS). The strength of this response declined as the winter progressed and there was some evidence for an adaptation or desensitization effect or even loss of interest by participants. Lawther et al. commented that these responses could have resulted from brief exposure to maximum concentrations several times the 24-hr average.

Studies of Bronchial Asthma. Some studies of pollution and asthma have reported negative or equivocal results (*36*, *37*). However, Cohen et al. (*38*) found a weak association between air pollution and the frequency of asthma attacks in a study of patients living near a coal-fueled power plant in West Virginia. Temperature was most strongly correlated with frequency of attacks among 20 patients having at least one attack during the study. In a multiple regression analysis, either SO_2 or TSP concentration was significantly correlated with attack rate after adjustment for temperature ($p < 0.01$). When days were classified as high and low particulate concentration (above or below 150 $\mu g/m^3$ TSP), or as high and low SO_2 concentration (above or below 200 $\mu g/m^3$), symptom prevalence was significantly higher on the high pollution days.

These values should not be interpreted as threshold values, since the dividing line seems arbitrary and the table comparing the two groups of days does not seem to be temperature adjusted. The authors provide little information about changes in panel membership over time, and also give insufficient information about their data analysis methods. In particular, they combined data from children and adults participating in the study. The sensitivity of asthmatics to exogenous allergens, respiratory infections, dust, animals, smoking, cold weather and psychological factors also suggests caution in attributing changes in symptom prevalence to changes in air pollution concentration.

Studies of Acute Respiratory Disease. Few studies relating acute exposure to moderate levels of air pollution to increased incidence of acute respiratory disease have been published. Although early studies by Dohan and Taylor (*39*) and Dohan (*40*) found an association between the level of suspended sulfates and work absences for respiratory disease among outdoor telephone workers, Ipsen et

al. (41) conducted a near replication of their study and found that apparent associations between absenteeism and air pollution were eliminated by adjustment for temperature, humidity and wind velocity.

Studies of Pulmonary Function. Van der Lende et al. (43) obtained results in a study of respiratory symptoms and lung function in the Netherlands which could represent an acute effect of air pollution. Examination of a large general population group in 1969 and again in 1972 failed to show the expected small decrease in levels of Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV_1), but rather small significant increases. The authors suggested that this could be attributed to improvement in air quality, from reported maximum 24-hr smoke level of 160 $\mu g/m^3$ (BS) and SO_2 concentration of 300 $\mu g/m^3$ in 1969 to 40 $\mu g/m^3$ (BS) and 100 $\mu g/m^3$ (SO_2) in 1972. [This and some other continental European studies used OECD calibration curves to express Black Smoke in $\mu g/m^3$. Some reviewers have suggested that the reported values should be increased, perhaps by a factor of 2, to be comparable with the British Black Smoke method (42).]

Expected decreases in pulmonary function were seen in a rural area measured at the same times. The authors explored possible sources of bias in the study but were unable to explain their results on that basis. If real, these changes are most reasonably interpreted as an acute, reversible response to elevated concentrations of air pollution.

Stebbings et al. (44) studied pulmonary function in 272 children during and after an air pollution alert in Pittsburgh in 1975. The 24-hr average SO_2 concentration reached 350 $\mu g/m^3$ and the 24-hr TSP level reached 770 $\mu g/m^3$. The mean $FEV_{0.75}$ and FVC values, instead of increasing as hypothesized, declined throughout the six-day period. Because the investigators did not have a pre-alert lung function measurement, the values obtained during the alert days could not be compared to "normal" lung function values. Since the children were followed for only the week, the possibility of a later increase in lung function values could not be excluded.

In a later report, Stebbings et al. (45) identified a group of children whose lung functions showed large increases after the alert. Since the proportion of such children was significantly greater in the alert than in a control area, they concluded that the alert had been associated with reduced lung function. Since the analysis was selected in response to the data, was based on unvalidated methodology, and failed to explain the anomalous finding of an excess of children in the alert area whose lung function declined during the study, these results do not provide sound evidence for health effects of air pollution at the levels reported.

Health Effects of Chronic Exposure to Sulfur Oxides and Particulate Matter

Studies of health effects of chronic exposure to air pollutants are typically cross-sectional, comparing mortality or morbidity rates within or among a number of communities. The possibility that the estimates of air pollution effects will be biased by other community differences related to health is particularly great in these studies. Concentrations of air pollutants are usually higher in urban than in rural areas, and many authors have noted that smoking patterns, family size, age distribution, occupation, domestic crowding, nutrition, physical activity and other characteristics of the population can differ between rural and urban areas. Although some studies have sought to match communities on important characteristics or use multivariate adjustment techniques to control for the effects of these factors, their effectiveness is typically unknown. This is especially true when complex regression models are used for adjustment, for the adjustment is limited by the degree to which the model correctly specifies the relation between these factors and the outcome under study.

Mortality Effects of Chronic Exposure to Sulfur Oxides and Particulate Matter

The study of Buck and Brown (46) was one of the first to show an association between annual average concentration of SO_2 and Black Smoke and mortality rate across communities in Great Britain. However, mortality data were obtained in 1955-59 and pollution was measured in 1962. Pollution levels were falling during this period. Although it has been argued that mortality effects were seen in boroughs where Black Smoke and SO_2 levels exceeded 200 $\mu g/m^3$, it is likely that exposures prior to and during 1955-59 were somewhat higher than in 1962. Wicken and Buck (47) also found differences in lung cancer and bronchitis mortality rates between areas of high and low pollution after adjusting for age, smoking habits and social class. However, this study was also limited by unavailability of concurrent air pollution measurements in most of the communities studied.

More recently, several investigators have used multivariate regression techniques to analyze mortality data obtained from vital statistics sources. The following sections discuss these investigations.

Analyses of Total Mortality Rates

As noted above, there are many reasons why mortality rates vary among communities. Therefore, study units should be selected to minimize variation due to factors other than air pollution. On the other hand, study units must be selected to conform with the available data. For mortality studies, Standard Metropolitan Statistical Areas (SMSA's) and cities meet this condition but present several difficulties. Investigators, recognizing that the study units differ with respect to factors other than air pollution, attempt to adjust for these differences by including socioeconomic and demographic variables in their analysis. Nevertheless, it is likely that the effects of variables such as personal habits, occupational exposure, and medical care cannot be fully quantified and eliminated in this way. If any of these factors covaries with air pollution levels, a spuriously large effect will be attributed to air pollution.

The evidence in a multiple regression analysis relating mortality to pollution can be expressed through the coefficients of the pollutants and their standard errors. Comparison of the results of regression analyses from major studies relating mortality rates to pollution levels across communities illustrates the problems that arise in interpreting these studies.

The four regression equations summarized in Table 10 are taken from the work of Lave and Seskin (*48*). TSP represents the average of 26 biweekly measurements of 24-hr TSP in each SMSA, while SO_4 is the lowest sulfate determination from these 26 observations. Regressions LS1 and LS2 were both obtained from the analysis of 1960 mortality data for 117 SMSA's. The two regression equations differ only in that the second contains one additional adjustment variable, home heating fuel. Adding this variable reduces the coefficients of the air pollutants by a factor of three and they are not significant in LS2. Lave and Seskin argue that this occurs because home heating fuels are a major pollution source, home heating fuels and pollutants are highly correlated. This contrast illustrates one effect of collinearity on the regression coefficients. Regression LS3 results from fitting the model from regression LS1 to 1961 data. Mortality and pollution values were about the same in the two years, and the coefficients are quite similar also. When the same model is fitted to the 1969 data (regression LS4), the estimated effects are larger even though mean TSP level declined from 118 $\mu g/m^3$ to 96 $\mu g/m^3$ and the average SO_4 level declined from 4.72 $\mu g/m^3$ to 3.46 $\mu g/m^3$. These comparisons show how sensitive these multiple regression analyses are to variable selection, and also raise questions of consistency.

Table 10. Coefficients of TSP and SO_4 in four regressions reported by Lave and Seskin.[a]

Regression	Source	Coefficient (SE)		Other variables[b]
		TSP	SO_4	
LS1	Data from 117 U.S. SMSA's in 1960	0.452 (0.169)	6.31 (2.33)	D, A, R, I, P
LS2	Data from 117 U.S. SMSA's in 1960	0.171 (0.158)	1.84 (2.16)	D, A, R, I, P, HHF
LS3	Data from 117 U.S. SMSA's in 1961	0.516 (0.178)	4.56 (2.49)	D, A, R, I, P
LS4	Data from 117 U.S. SMSA's in 1969	0.818 (0.241)	7.74 (3.67)	D, A, R, I, P

[a]Data of Lave and Seskin (*48*).
[b]Symbols used in this column are defined in Table 12.

Table 11. Coefficients of TSP and SO_4 in regressions analysis by Lipfert and Crocker et al.

Regression	Source	Coefficient		Other variables[a]
		TSP	SO_4	
L1	Data from 60 U.S. SMSA's in 1969[b]	0.78	5.4	D, A, R, I
L2	Data from 60 U.S. cities in 1969[b]	0.78	8.2	D, A, R, I
L3	Data from 136 U.S. cities in 1969[b]	1.00	-2.0	A, R, I, H, B
L4	Data from 181 U.S. cities in 1969[b]	0.72	-4.3	A, R, I, H, B, C, log D
C1	Data from 60 U.S. cities in 1960[c]	0.11	-0.31[d]	MD, MI, E, CH, C, CT, R, MA, DF

[a]Symbols used in this column are defined in Table 12.
[b]Data of Lipfert (*49, 50*).
[c]Data of Crocker et al. (*51*).
[d]Coefficient of SO_x.

Results of four regression analyses reported by Lipfert (*49*, *50*) are shown in Table 11. The first (L1) is based on analysis of 1969 mortality data from 60 U.S. SMSA's, using a model much like regression LS4 in Table 10. Very similar coefficients are obtained. The first two models in Table 11 differ only in that the first uses mortality data from 60 SMSA's while the second uses mortality data from 60 U.S. cities. The coefficient of SO_4 is larger in the second regression using smaller geographic areas. Model L3 differs from L2 in that more cities are included and age of housing and birth rate are added as independent variables, while cigarette consumption is added in L4. Though the coefficient of TSP changes very little, the coefficient of SO_4 is negative in these regressions.

The final regression in Table 11 is taken from an analysis of 60 U.S. cities in 1970 by Crocker et al. (*51*). In addition to variables used by other investigators, this model includes variables for climate, education, availability of medical care and nutritional habits. Although Crocker uses SO_2 and not SO_4 as a pollution variable, neither pollutant contributes significantly to the regression. Crocker et al. report a correlation between SO_2 and SO_4 of 0.74.

The association between air pollutant concentration and mortality rates in different analyses can be summarized by the elasticity. An elasticity is a dimensionless number that represents the expected percent change in the dependent variable, mortality, associated with a 100% increase from the mean value in each of the pollutant variables in the regression. Elasticity is computed by multiplying each air pollutant regression coefficient by the average value of that pollutant in the data set, adding these quantities for all pollutants, and dividing by the average mortality over study units. So long as the set of pollution variables chosen contains variables capturing the total association between all air pollutants and mortality, the elasticity will be relatively insensitive to the choice of a subset of these highly collinear pollutant variables. Thus, the elasticities can be viewed, at least approximately, as measuring the total mortality effect of all pollutants included.

Table 13 gives elasticities for the nine regression analyses summarized in Tables 10 and 11. Regressions LS1, LS3, and LS4 were the simplest models used by Lave and Seskin and had the largest elasticity. In regressions using more variables, such as home heating fuel in regression LS2, smaller elasticities were obtained. (When occupation was added to the model for regression LS1, elasticity declined to 0.05). Regressions L1 and L2 included population density, percentage above 65, percentage nonwhite and percentage with income below $3,000 as independent variables. When birth rate and age of homes were added (L3) or cigarette smoking (L4), elasticity declined to 0.06 and 0.04, respectively. The effect of cigarette smoking should especially be noted. Finally, in the analysis by Crocker et al. (*51*) using several other added independent variables (C1), the elasticity was nearly zero. These variables included measures of medical care, diet, climate and cigarette consumption and could easily be defended as critically important in any analysis controlling for other factors expected to influence mortality.

Though it has sometimes been argued that smoking is not associated with air pollution concentration, Crocker et al. report a correlation of 0.23 between cigarette consumption and sulfur dioxide in the 60 cities in their study. Certainly the two variables are not causally related, but both may reflect other characteristics of the population.

Schwing and McDonald (*52*) report on a study of

Table 12. Definitions of other independent variables used in multiple regressions in Tables 10 and 11.

Variable	Definition
D	Population density in person/mile^2
A	Percentage of population 65 or older
R	Percentage of population nonwhite
I	Percentage of population with income below $3000/year
P	Log arithm of SMSA population
HHF	Percentage of homes using each of several home heating fuels
H	Percentages of housing units built before 1960
B	Births/1000 population/year
MD	No. of physicians per capita
MI	Median income
E	Percentage of persons 25 or older with high school diploma
CH	Percentage of persons living in homes with more than 1.5 persons per room
C	No. of cigarette packs purchased per capita
CT	No. of days with temperature below 0°C
MA	Median age

Table 13. Elasticities for air pollutants in nine regression analyses of mortality.

Regression	Elasticity
LS1	0.09
LS2	0.03
LS3	0.09
LS4	0.12
L1	0.10
L2	0.09
L3	0.06
L4	0.04
C1	0.004

ated with cigarette smoking at these ages. Because ution concentrations in 1962 were presumably n lower than those in earlier years, the concen- ons cited probably understate the exposure of participants. We note that exposure during hood to air pollution concentrations in excess of 130 $\mu g/m^3$ (BS) and 130 $\mu g/m^3$ (SO_2) resulted in no significant increase in respiratory illness by adulthood compared to those exposed to lower air pollution concentrations.

Lambert and Reid (*61*) mailed self-administered questionnaires to 18,379 men and women in Britain to assess the relationship of smoking and air pollution to bronchitis symptoms. The reply rate was 74% from the 35-69 year-old age group studied. From the 9,975 replies analyzed, the authors conclude that the prevalence of respiratory symptoms increased with pollution levels independently of cigarette smoking. Air pollution was found to have a greater effect on the symptoms of smokers than nonsmokers, in terms of the absolute difference in symptom prevalence rates.

The exposure levels in this study are approximate, since only 30% of the population surveyed was covered by actual air pollution measurements. The pollutants measured, BS and SO_2, were taken from 1965 data of the British National Air Pollution Survey. The balance of the population was assigned to exposure categories based on the Douglas-Waller (*58*) index which was developed from 1952 domestic coal consumption. A comparison of symptom-prevalence ratios from measurements of BS, SO_2, and index values shows similar ratios and similar gradients for symptoms with increasing pollution. The lack of complete air pollution data adds uncertainty to the exposure estimates, but in those areas where BS and SO_2 measurements were available, increased prevalence of symptoms was found in association with BS and SO_2 levels between 100 and 150 $\mu g/m^3$, as an annual average.

Polish Studies. A study of two areas of contrasting air quality in Cracow, Poland, was conducted by Sawicki. The study began with a cross sectional survey in 1968 and continued with a prospective study until 1973 (*62*). Annual average particulate values in 1968 were 90 and 170 $\mu g/m^3$. In 1968, chronic bronchitis prevalence was greater in the more polluted area for men, but not for women. The difference was statistically significant for men who were nonsmokers or present smokers. These data are given in Table 16. Asthmatic disease prevalence was also greater among smokers living in the more polluted area and FEV_1 as a percentage of FVC was lower for most age-sex-smoking-history groups.

Between 1968 and 1973, the annual mean concentration of SO_2 and BS declined slightly for Cracow as a whole but increased slightly at the sites close to the homes of most study participants. In 1973, respiratory disease was again more prevalent among those living in the areas of high pollution for many, but not all of the age, race, and sex groups studied. Mean FEV_1 level was not significantly different in the two areas. The prevalence of obstructive disease was higher in the more polluted area only for present smokers. The authors concluded that smoking and, to a lesser extent, occupational exposure and age had the greatest effect on respiratory illness prevalence, while air pollution at the place of residence was listed as one of several factors having a smaller effect on respiratory illness.

Rudnik et al. (*63*) reported extensively on the early phase (1970-1976) of a long-term study of the factors which influence development of childhood

Table 16. Prevalence of chronic bronchitis by sex and smoking status in 1968.[a]

	Low pollution area						High pollution area					
	Men			Women			Men			Women		
Smoking status	N[b]	P[c]	SE[d]	N	P	SE	N	P	SE	N	P	SE
Total	323	11[e]	1.7	362	4	1.0	262	19[e]	2.4	396	5	1.1
Nonsmokers	56	4	2.6	286	2	0.9	58	7	3.4	264	3	1.0
Ex-smokers	46	4	2.9	18	11	7.4	40	5	3.4	34	6	4.1
Present smokers	221	14[e]	2.3	78	10	3.4	164	27[e]	3.5	98	10	3.0
Period of smoking												
1-10 years	56	5	2.9	41	7	4.0	42	7	3.9	42	5	3.4
11-20 years	89	9[e]	3.0	21	14	7.6	38	29[e]	7.4	18	6	5.6
> 21 years	76	28	5.2	16	13	8.4	84	36	5.2	38	18	6.2

[a] Data of Sawicki (*62*).
[b] Number of persons studied.
[c] Prevalence of chronic bronchitis.
[d] Standard error of the observed rate.
[e] Rates which are significantly different at the 0.05 level.

prevalence and on potentially confounding factors such as cigarette smoking and occupation. Nevertheless, when only a few observations have been made at different air pollution levels, it is difficult to construct generalizable quantitative dose-response relationships.

The major studies suggesting morbidity effects of exposure to elevated concentrations of particulate matter and/or sulfur oxides have been reported from three countries; Great Britain, Poland and the Unites States.

British Studies. Lunn et al. (*56*, *57*) studied schoolchildren living in four areas of Sheffield, England with different air pollution concentrations. These concentrations are shown in Table 14 for the two winters studied. Questionnaires were answered by parents and the investigators found substantially higher prevalence of symptoms of respiratory disease in the three more polluted areas than in the less polluted area (Table 15). These children were followed up in 1967-69 when they were nine years old (*57*). As a result of the institution of smoke control, smoke levels were reduced to about half their former levels. When children from the three dirtier areas were pooled and compared to children from the clean area in the second study, there were no differences in symptom prevalence rates. Pollution concentrations in the later period were 48 $\mu g/m^3$ (BS) and 123 $\mu g/m^3$ (SO_2) in the clean area and averaged about 140 $\mu g/m^3$ (BS) and 200 $\mu g/m^3$ (SO_2) in the dirty areas.

Douglas and Waller (*58*) reported on a study of a sample of children born during one week in March 1946. Air pollution was assessed by creating an index based on coal consumption. The authors created four pollution categories, and found that the prevalence of lower respiratory disease, but not upper respiratory disease increased with increasing pollution when the children were studied at ages 6, 7, 11 and 15.

Comparison of the index to measured BS and SO_2 concentrations in 1962 established a gradient of mean annual pollutant concentrations across the four pollution categories. The lowest pollutant concentrations in 1962 among the categories with increased morbidity were 130 $\mu g/m^3$ (BS) and 130 $\mu g/m^3$ (SO_2). Colley et al. (*59*) followed this cohort at age 20, and Kiernan et al. (*60*) followed it again at age 25. Neither investigation found an association of respiratory disease symptom with previous air pollution exposure, although at age 20 the prevalence of respiratory symptoms was slightly higher among those who had lived in high pollution areas (11.5%) than among those from low pollution areas (10.2%), and a similar relationship was found at age 25. Respiratory symptom prevalence was associ-

Table 14. Air pollution concentrations in communities studied by Lunn et al.[a]

	Concentration (24-hr average), $\mu g/m^3$							
	Greenhill		Longley		Park		Attercliffe	
	1964	Winter 1965-66	1964	Winter 1965-66	1964	Winter 1965-66	1964	Winter 1965-66
BS	97	(70–78)	230	177	262	220	301	249
SO_2	123	(109–134)	181	194	219	241	275	301

[a]Data of Lunn et al. (*56*).

Table 15. Symptoms by area in the study of Lunn et al.[a]

	Greenhill			Longley			Park			Attercliffe		
Symptom	N[b]	P[c]	SE[d]	N	P	SE	N	P	SE	N	P	SE
Nasal discharge	408	6.4	1.2	192	5.2	1.6	130	15.4	3.2	82	14.6	3.9
≥ 3 colds	413	34.4	2.3	194	43.8	3.4	130	48.5	4.4	82	46.3	5.5
Eardrum finding	381	9.4	1.5	178	10.7	2.3	125	14.4	3.1	75	17.2	4.4
Frequent cough	411	22.9	2.1	194	36.1	3.4	130	34.6	4.2	82	50.0	5.5
Cold going to chest	412	34.7	2.4	194	42.8	3.6	130	40.0	4.3	82	53.7	5.5
Lower respiratory infection	413	23.0	4.3	192	36.0	5.8	127	35.0	7.1	82	30.0	9.2

[a]Data of Lunn et al. (*56*).
[b]The number of responses obtained.
[c]The percentage of positive responses.
[d]The estimated standard error of the observed percentage.

46 SMSA's (1959-61) in which 23 explanatory variables are used, including climate, socioeconomic, occupational and smoking variables and eight air pollutants. This study differs from those summarized in Tables 10 and 11 in that the investigators included all 23 variables in their models. To counter severe collinearity, the authors used two methods of analysis, ridge regression and constrained least squares, rather than ordinary least squares. (The previously reported studies all used ordinary least squares.)

Ridge regression is a numerical method for stabilizing estimates of regression coefficients from a data set that has collinear explanatory variables. While the method does achieve stability, it does so by selecting an arbitrary constant that has the effect of shrinking each estimated coefficient toward zero. Though ridge regression leads to smaller standard errors for the estimated coefficients, these coefficients are no longer interpretable as partial regression coefficients, that is, measures of the effects of changes in a single variable while the other variables are held fixed. As emphasized throughout this presentation, collinear data sets are fundamentally insufficient to allow assignment of mortality effects to individual members of a group of collinear explanatory variables.

Schwing and McDonald also use constrained least squares, constraining the air pollution coefficients to positive values. This may be unreasonable when eight air pollutants are studied simultaneously. Thurston et al. (53) report that respirable sulfate as a fraction of total sulfate is not constant over different levels of air quality. They note that in "dirty" cities the fraction is 0.6 to 0.7 while in "clean" cities the fraction is 0.8 to 0.9. Thus, if the respirable sulfate affects mortality, an indicator of overall air quality such as TSP could take a negative sign, when both TSP and respirable sulfates are included in the model, to account for the difference in the respirable sulfate fraction between cities.

Schwing and McDonald report an elasticity of 0.22 from ridge regression and an elasticity of 0.045 from constrained least squares. These values are still an order of magnitude larger than that reported by Crocker et al. (0.004).

This discussion has been provided to illustrate the limitations of multiple regression analyses of vital statistics data, using explanatory variables defined by data availability rather than intrinsic interest, and complicated by severe collinearity of pollutant and other explanatory variables. The model can only be approximately correct, the surrogate explanatory variables can never lead to an adequate adjusted analysis, and it is impossible to separate associations of mortality rate with pollutant and confounding variables. This group of studies, in our opinion, provides no reliable evidence for assessing the health effects of sulfur dioxide and particulate matter.

Morbidity Effects of Chronic Exposure to Sulfur Oxides and Particulate Matter

This section focuses on those studies that provide the air pollution and health-status data necessary to assess the morbidity effects of chronic exposure to sulfur oxides or particulates. These studies most commonly represent the cumulative exposure to air pollutants as an arithmetic average concentration of sulfur compounds and particulates during an interval including the study period. Since chronic exposure may refer to the lifetime of an individual, this measure of exposure may be misleading when pollution concentrations have changed substantially during the years preceding the study. Morbidity outcomes are generally limited to respiratory symptoms and measured lung function. Respiratory symptoms are most commonly assessed with self- or interviewer-administered questionnaires. The standard questionnaire developed by the British Medical Research Council (54) has been used typically, with modifications or additions. [A standard questionnaire has recently been developed under the joint sponsorship of the American Thoracic Society and the Division of Lung Diseases, National Heart, Lung and Blood Institute, and is recommended for all U.S. population studies (55).] Lung function is generally measured by spirometry from which both forced expiratory volume and flow rates can be determined. Relationships between air pollution and nonrespiratory or systemic morbidity are usually not explored.

Most of the studies reviewed are cross-sectional investigations of morbidity prevalence. Many of the difficulties of inferring a cause-effect relationship between air pollution and health outcome in such studies have been discussed above. Typically, a few cities or areas with different air pollution concentrations are compared. The study populations are either matched on, or analyses standardized for, differences in variables such as age distribution, race, socioeconomic characteristics, occupational categories, and smoking habits. Often only two cities or areas with contrasting air quality are compared. Rarely are more than half a dozen areas compared. The effect of limited observations at differing air pollution levels is partially mitigated by the ability to gather extensive information on outcome variables such as ventilatory function and symptom

chronic nonspecific respiratory disease (CNSRD). The authors discussed an early pilot study that was used to test and develop the design and instruments for the main study. The main study, scheduled for completion in 1982, compares 3805 eight to ten year olds, on respiratory symptoms, illness, and lung function (PEFR), in the Polish communities of Cracow (two areas), Nowy Targ, and Limanowa. The arithmetic mean air pollution values for each of two years in these communities are shown in Table 17. The authors provide detailed information on the distribution and seasonal pattern of the air pollution observations.

Most of the symptoms analyzed and past respiratory illness were less prevalent in the cleaner communities of Nowy Targ and Limanowa than in the two areas in Cracow. There was some indication that symptom rates were lower in the cleanest city of Limanowa than in Nowy Targ. Peak expiratory flow rate (PEFR) was lower in Cracow. In fact, PEFR of children without symptoms in Cracow was lower than in symptom-positive children in the cleaner areas. The authors concluded that living in the more polluted community had a deleterious effect on respiratory symptoms, illness, and lung function. The effect of living in Cracow was greater than the other social, economic and environmental factors investigated by the authors. Unfortunately, PEFR as measured with Wright peak flow meters is subject to considerable variation due to variability between machines. It is not clear from these reports how this phenomenon was controlled.

U.S. Studies. A series of studies conducted in a New Hampshire pulp mill town, beginning in 1961, represent some of the earliest work on the health effects of chronic exposure to sulfur oxides and particulates in this country. In the initial study, Ferris and his colleagues (*64*, *65*) compared symptom prevalence and lung function in three areas with different pollution levels within Berlin, New Hampshire and found no associations after control for cigarette smoking. In a subsequent study (*66*), a random survey was carried out in the relatively clean city of Chilliwack, British Columbia. Though the pollution levels were considerably lower than those in Berlin, the prevalence of chronic respiratory disease was not significantly different in the two towns after adjustment for age and smoking habits.

The average values of FEV_1 and peak expiratory flow rate (PEFR) were higher in Chilliwack than in Berlin for 30 of 32 subgroups defined by sex and smoking history after controlling for age and height. The authors suggested that differences in ethnicity, weather, medical facilities and other factors may have confounded the examination of the effect of air pollution.

The Berlin, New Hampshire population was followed up in 1967 and again in 1973 (*67-69*). During the period between 1961 and 1967, all measured indicators of air pollution fell. In the 1973 follow-up, sulfation rates nearly doubled from the 1967 level (0.469 to 0.901 mg SO_3/100 cm^2/day) while TSP values fell from 131 to 80 $\mu g/m^3$ (Table 18). Concentrations of SO_2 were estimated by assuming that all atmospheric sulfur was in the form of SO_2. For all three periods, concentrations of SO_2 at these sites were below the present annual ambient air standard.

During the 1961 to 1967 period, standardized respiratory symptom rates decreased and there was an indication that lung function also improved. Thus, the higher pollution concentrations seen in 1961 were judged to be associated with increased incidence of respiratory symptoms and impairment of lung function. Between 1967 and 1973, age-sex standardized respiratory symptom rates and age-sex-height standardized pulmonary function levels were unchanged. The authors concluded that either

Table 17. Two-year mean air pollution values.[a]

	SO_2 $\mu g/m^3$		BS, $\mu g/m^3$	
	1974	1975	1974	1975
Cracow-1	111.4	108.1	169.7	150.9
Cracow-2	138.2	148.5	204.9	227.4
Nowy Targ	57.1	66.8	82.0	79.8
Limanowa	41.5	64.3	53.4	49.2

[a]Data of Rudnick et al. (*68*).

Table 18. Pollution levels, Berlin, New Hampshire, during three study periods.

Year (s)	Total dustfall, g/m^2/30 days	TSP, $\mu g/m^3$	Sulfation (lead peroxide), mg SO_3/100 cm^2/day	Sulfation converted to SO_2, $\mu g\ m^{3a}$
1961	18.4	180	0.731	55
1966–67	14.3	~131	0.469	37
1973	—	80	0.901	66

[a]Assuming all sulfur in the form of SO_3.

the change in air pollution concentration during the latter period was not associated with a change in respiratory health or that the study was too small to detect an effect. The comparison of health status between 1961 and 1967 suggests morbidity effects at 180 $\mu g/m^3$ (TSP) and 55 $\mu g/m^3$ (SO_2). These effects could represent a combination of transient (acute) and irreversible (chronic) effects of air pollution exposure. The TSP value of 180 $\mu g/m^3$ was based on sampling during the summer months and probably underestimated the annual average concentration. The comparison of 1967 to 1973 is uninformative because of offsetting changes in pollution concentrations, although SO_2 concentrations were below present ambient standards in both periods.

Mostardi and Leonard (*70*) compared the results of pulmonary function testing in 42 high school students from an urban area with pollution concentrations of 100 $\mu g/m^3$ (SO_2) and 109 $\mu g/m^3$ (TSP) and 50 students from a rural area with pollution concentrations of 72 $\mu g/m^3$ (SO_2) and 83 $\mu g/m^3$ (TSP) (maximum annual average over five years). This study was flawed by failure to consider smoking effects.

Subsequently, Mostardi and Martell (*71*) reported on 173 and 161 students respectively from the same urban and rural areas. They tested FVC and $FEV_{0.75}$ on subjects residing for 4 years or more in the areas. The groups were analyzed separately by sex and nonsmoking males were separately considered. The two groups had similar anthropometric characteristics. Approximately 20% lower values of $FEV_{0.75}$ and 10% lower values of FVC were reported in the more polluted area for the total group, for males, females, and for non-smoking males. While a higher proportion of smokers was found in the urban area (12% vs. 6% in the rural area) the authors claim this did not influence their results. They did not mention race in this study. In the first report (*70*) the authors found that the lung function differences persisted after exclusion of the three black students in the urban area.

The observed differences of 20% for $FEV_{0.75}$ and 10% for FVC in two communities with relatively small differences in ambient concentrations of SO_2 and TSP are striking. Other studies discussed here suggest that air pollution at these levels would not have this large an impact on lung function. This implies that other community differences such as racial composition or socioeconomic status may have contributed to the intercommunity differences. The observed differences cannot be reliably attributed to differences in air pollution concentrations.

The remainder of the evidence for health effects of sulfur oxides and particulate matter comes from the Community Health and Environment Surveillance System (CHESS) program, sponsored by the Environmental Protection Agency during the late 1960's and early 1970's. Much of this work was published in a monograph (*72*) and subsequently summarized in three brief papers (*73-75*). These studies have been severely criticized. The most important criticism is that methodology and quality control for aerometric measurements was seriously flawed. In particular, spills of reagent and other errors in handling measuring equipment led to underreporting of SO_2 values by 50 to 100%, while smaller biases were identified in the procedures for particulate measurement, resulting in underreporting by an estimated 10 to 30%. A number of other problems of study design, participant follow-up and data quality control were detected, raising doubts about the accuracy and proper interpretation of reported results. Ultimately, the CHESS studies were the subject of a special Congressional hearing (*76*) and an investigation by an expert panel convened by a Committee of the U.S. House of Representatives (*77*). The principal criticism of the CHESS report arising from this review was that the data had been overinterpreted in the CHESS monograph.

As we have indicated, observational studies of the health effects of air pollution are particularly difficult to conduct because individual exposure is poorly measured and populations may not be comparable in ways related to respiratory health. In view of the special problems occurring in the studies published in the CHESS monograph and the failure of subsequent publications to meet these criticisms, we believe that these studies cannot be used to assess the exposure response relationship between sulfur oxide and particulate concentrations and morbidity. This decision substantially reduces the evidence for morbidity effects of chronic exposure to particulates and SO_2 at levels near present air quality standards, in that most of these studies reported health effects in association with pollutant concentrations near these standards. A more extensive discussion of this controversy can be found in the above cited congressional reports and a recent review article (*78*).

Two studies which were part of the CHESS program were published separately (*79, 80*). Information in these articles addresses some of the criticisms of the CHESS program. Hammer et al. (*79*) surveyed children in four metropolitan New York communities chosen for socioeconomic similarity.

Some of the aerometric data used in Hammer's analysis are shown in Table 19. The TSP values for 1968-70 were obtained by extrapolating from the TSP values at the Manhattan station using dustfall values in each borough and the ratio of dustfall to TSP at the Manhattan station. Values of SO_2 in

Table 19. Approximate air pollution concentrations.[a]

Pollutant		Air pollution concentration, μg/m³ 1968-1970	1971	1972
SO_2	Riverhead	N/A[b]	23	22
	Queens	175	51	50
	Bronx	250	51	38
TSP	Riverhead	N/A[b]	34	36
	Queens	85	63	89
	Bronx	110	86	60

[a]Data of Hammer et al. (*79*).
[b]Not available.

Queens and Bronx were obtained from stations in the boroughs. Data for Riverhead were provided by Suffolk County (New York). The fourth community, Sheepshead, was geographically contiguous to the area studied in Queens, and was assumed to have similar pollution values. All data for 1971 and 1972 were obtained from the CHESS monitoring network. Although Riverhead unquestionably had substantially less air pollution than the other three communities, both historically and during the study, the values cited can be regarded only as approximations to the ambient concentrations in the study communities. Questions on respiratory disease were answered retrospectively by parents. Significant differences were found in rates of lower respiratory disease in the low pollution community compared to the three high pollution communities for all ages from 1 to 12. Sex and education of head of household were considered in the analysis. Although smoking may have been a factor in older children, this study suggests morbidity effects at pollution concentrations of about 175 μg/m³ (SO_2) and 85 μg/m³ (TSP), using the average of the annual exposures over the years 1968 to 1970.

Interpretation of this study is complicated by a 10-fold decline in SO_2 and 3-fold decline in TSP over the 12 year period and by the lack of direct local measurement of air pollution concentration. More detailed information might improve exposure estimation for each child by age and period of exposure.

Hammer (*80*) also conducted a retrospective study, using parent-answered questionnaires covering four years recall of acute lower respiratory disease in 10,000 children aged 1 to 12 years. The two communities chosen for comparison differed in particulate air pollution concentration but had low SO_2 concentrations (Table 20).

The values for 1968-1970 cited in Table 20 were obtained by fitting trend lines to a few data points. As with the New York study, we can be confident that the cleaner community (Charlotte) had lower TSP concentrations, while in this study both communities had very low SO_2 concentrations. However, the TSP concentrations cited are approximate.

Hammer found that lower respiratory disease morbidity was less prevalent for children in the cleaner community (Table 21). A separate analysis of children with bronchial asthma produced more equivocal findings.

Among asthmatics, morbidity rates in the more polluted community were greater for only about half of the comparisons made. In the case of asthmatic blacks, bronchitis rates were greater in the cleaner community. On the whole, this study showed an association between TSP concentration and morbidity level.

Among the remaining studies in the CHESS program, the study of chronic respiratory disease prevalence in the Salt Lake Basin (*81*) is deserving of further attention. Although large and statistically significant differences were found in disease prevalence between communities with high and low levels of SO_2 and sulfates, these pollutants were among those found to be especially inaccurately measured by the CHESS aerometric network, and Utah State Aerometric was incomplete for the relevant years. Nevertheless, the health data have not been convincingly criticized, and an air pollution gradient was recognized to exist across the study communities, despite problems of precise measurement. Further work with these data may increase the acceptance of this study.

At the August 1980 meeting of the Clean Air Scientific Advisory Committee, EPA officials reported that unacceptably high data entry error rates had been detected in some CHESS data sets, and that data sets for the major CHESS studies would be reentered and reanalyzed to establish the validity of earlier results reported from the CHESS program. Unfortunately, this report further weakens the credibility of CHESS results. Although we cite results from two CHESS studies, continued use of these findings is contingent upon successful validation of the data sets by the staff of the EPA.

The studies that have been reviewed in this section provide the observational evidence for mor-

Table 20. Approximate air pollution values for Birmingham and Charlotte, 1968-71 average.[a]

Pollutant	City	Air pollution values, μg m³ 1968-70	1971
TSP	Charlotte	<25	<25
	Birmingham	<25	<25
SO_2	Charlotte	81	74
	Birmingham	141	133

[a]Data of Hammer (*80*).

Table 21. Age-adjusted rates (%) of one or more episodes of lower respiratory disease, by race and age interval.[a]

Race	Age, yr	Any lower respiratory Disease, %		Bronchitis, %	
		Charlotte	Birmingham	Charlotte	Birmingham
White	1–4	35.0	38.9	23.1	27.7
	5–8	29.9	36.3	20.4	26.2
	9–12	22.0	26.4	14.9	18.6
Black	1–4	27.8	24.0	13.7	10.6
	5–8	16.4	20.6	7.8	7.9
	9–12	12.7	15.9	6.3	6.9

[a]Data of Hammer (*80*).

bidity effects of chronic exposure to SO_2 and particulate matter. In the next section, we summarize and interpret all of the evidence for health effects of acute and chronic exposure.

Summary and Conclusions

Individual studies providing evidence on the association between health effects and the ambient concentration of sulfur oxides and particulate matter have been described in preceding pages. This section is devoted to a summary of that evidence in an effort to present a perspective on using the available data to establish concentrations for both acute and chronic exposure associated with increased morbidity or mortality. The analysis in this section has been influenced by the many thoughtful reviews published in recent years (*78*, *82-89*).

For the purposes of this discussion, acute exposure is measured by the 24-hr average concentration of each pollutant. Current National Ambient Air Quality Standards for maximum 24-hr average concentration are 260 $\mu g/m^3$ for TSP and 365 $\mu g/m^3$ for SO_2. Exposures over shorter periods may be important, perhaps as measured by the peak hourly concentration in each 24-hr period. Exposures calculated from different short term averaging periods are highly correlated in most situations.

The choice of method for measuring chronic exposure is less straightforward, and can have a significant influence on the determination of concentrations associated with health effects. Most studies reported arithmetic average concentrations of each pollutant over some sampling period including the study period. Although the sampling period did not cover an entire year in every instance, we express the values reported in the various studies as an annual mean concentration. Current National Ambient Air Quality Standards for annual mean concentration are 75 $\mu g/m^3$ for TSP (computed as the geometric mean of 24-hr samples) and 80 $\mu g/m^3$ for SO_2 (arithmetic mean). Since arithmetic means were used almost exclusively for reporting particulate and sulfur oxide concentrations in the studies of chronic exposure, these values have been used in summarizing the evidence. Differences between geometric and arithmetic means are usually unimportant compared to other sources of uncertainty in measuring exposure.

Many of the studies cited failed to obtain concurrent aerometric data. When available, those data were collected at one or a few sites distant from the homes of study participants. The air monitoring techniques were often primitive by current standards, with a resulting potential for substantial bias or variability in measuring concentration. Even when ambient concentrations are optimally measured, the implications for individual exposure are uncertain. Consequently, very great uncertainties about the actual air pollution exposures of study participants in most of the studies discussed weaken analyses of the relationship between exposure and health effect response.

For studies using Black Smoke (BS) to measure particulate concentrations, the conversion to TSP values is highly uncertain and depends upon conditions in the study environment. We convert BS to TSP values using the results of Commins and Waller (*89*). Since their study was conducted in London between 1955 and 1963, the applicability to other sites or times is unknown. Although we use their conversion to unify the discussion, this introduces additional uncertainty. For the one New York study using Coefficient of Haze (CoHs), we use the conversion developed in New York by Ingram and Golden (*90*). They equate 5 CoHs to 580 $\mu g/m^3$ (TSP).

Some studies have reported sulfate concentrations, and there has been considerable interest in the fine particulate fraction (*91*). However, the correlation between TSP concentrations and its components has been consistently high in observational studies. Thus, these studies provide no basis for separately assessing the health effects of different fractions by size or chemistry of ambient par-

ticulate matter. Further understanding of the proper measure of particulate concentration in terms of health significance will come from advances in understanding of lung physiology and from exposure studies with animals.

Assessing causal relationships from studies of association is a familiar problem for epidemiologists, and the problem is especially difficult in air pollution research. When exposures are near present air quality standards, the health effects of air pollution exposure are likely to be small. Many other individual characteristics influence lung function and the risk of respiratory disease. Some of these, like smoking, occupational differences, and socioeconomic status, are well known but difficult to measure, others like passive smoking have been recognized only recently. The association of lung function and respiratory disease with these characteristics is often much greater than the likely effects of air pollution. The possibility in any observational study that these factors have been inadequately controlled adds additional uncertainty to the interpretation of the nonexperimental studies. Thus, the determination of concentrations associated with adverse effects is tempered by recognition of these potential nonsampling errors.

For all of these reasons, the epidemiologic data base is extremely weak. In particular, it is insufficient to distinguish between a threshold hypothesis, that health effects are seen only above certain concentrations, and a monotonic exposure-response hypothesis, that health effects increase (perhaps very slightly) with air pollution concentration over a very wide range. Although we favor the latter hypothesis as more physiologically plausible, we have chosen to interpret the evidence in terms of concentrations at which health effects have been detected. These values should not be interpreted as threshold values. Finally, SO_2 and particulate concentrations were highly correlated in many of the studies cited. Thus we cite concentrations jointly of SO_2 and TSP at which health effects have been detected, and then discuss the evidence for health effects of the individual pollutants.

Health Effects of Acute Exposure to SO_2 and Particulate Matter

The studies providing evidence for health effects resulting from acute exposure to SO_2 and particulate matter are summarized in Table 22. The selection criteria excluded studies of SO_2 or TSP exposures above 1000 $\mu g/m^3$, and the list is strikingly short. The two mortality studies cited (from the same group) found increased mortality associated with TSP concentrations of 500-600 $\mu g\ m^3$ in conjunction with SO_2 concentrations of 300-400 $\mu g/m^3$. These studies summarize a relatively small body of data from two winters in London. The individual studies do not suggest a threshold phenomenon. Although there is some suggestion of an association at lower concentrations, the evidence is very scanty. For all of the reasons discussed above, this interpretation is subject to considerable uncertainty, and this explains in part the divergent views expressed by different reviewers. Time series analyses of daily mortality records over several years have sometimes suggested small mortality effects of air pollution concentrations at much lower concentrations, particularly in association with particulate concentration in the New York studies, but the results have been highly dependent on model selection and are internally inconsistent.

Only two reports of associations between morbidity and 24 hour average pollutant concentrations are cited in Table 22, and one of these is again the study by Martin. Thus, the acceptable epidemiologic evidence for health effects in association with acute elevations of SO_2 or TSP concentrations below 1000 $\mu g/m^3$ consists of only two studies. Other reports, including those of Cohen (*38*), Van der Lende (*43*), and Glasser and Greenberg (*27*) are suggestive but subject to numerous ambiguities related to meth-

Table 22. Summary of evidence for health effects of acute exposure to SO_2 and particulate matter.

Type of study	Reference	Effects observed	24-hr average pollutant levels at which effects were detected, $\mu g/m^3$	
			TSP	SO_2
Mortality	Martin and Bradley (*19*)	Increases in daily total mortality above the 15-day moving average	600	300
	Martin (*80*)	Increases in daily total mortality above the 15-day moving average	600	400
Morbidity	Martin (*80*)	Increases in hospital admissions for cardiac or respiratory illness	600	400
	Lawther et al. (*34*, *35*)	Worsening of health status among 195 bronchitics	350	500

odology and interpretation. Although severe air pollution episodes have frequently been associated with excess mortality and morbidity, there is only a small body of evidence to document such effects at concentrations below 1000 $\mu g/m^3$.

Health Effects Associated with Chronic Exposure to SO_2 and Particulate Matter

As noted above, the evidence for mortality effects of chronic exposure to SO_2 or particulate matter is inconclusive. Though several studies have found associations, the methodological uncertainties are so great as to make these studies essentially valueless for quantifying the exposure-response relationship. The morbidity studies that have found differences in levels of health effects in association with differences in pollutant concentrations are summarized in Table 23, and displayed in Figure 1. In these studies, upper and lower respiratory symptoms, chronic bronchitis and reduced pulmonary function were observed in association with TSP concentrations in excess of about 180 $\mu g/m^3$. In one study, acute respiratory disease was increased in association with reported TSP concentration of 135 $\mu g\ m^3$ though these values were estimated from relatively weak aerometric data. As with the studies of acute effects, most of these studies could be interpreted as demonstrating that the prevalence of adverse health effects increases monotonically with exposure over the entire range of exposure studied. These studies provide little evidence to assess the health effects associated with elevated SO_2 concentrations along with moderate particulate concentrations. Although Hammer (*79*) and the Salt Lake Studies (*72*) did report such associations, the problems with methodology and aerometric measurement in those studies limit their value in this assessment. Though exposure to these pollutants at concentrations below those cited may imply some increase in risks, it will be difficult to resolve this question in an observational setting, because health effects of pollutants at these concentrations are likely to be small relative to effects of other factors which vary over communities.

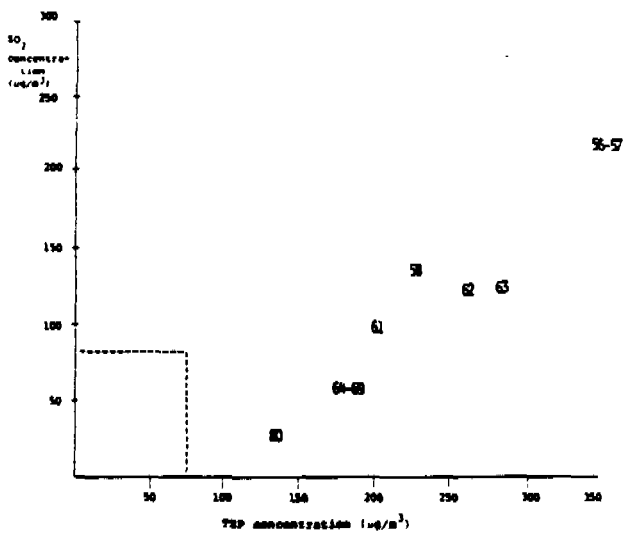

FIGURE 1. Plot of studies in which increased levels of adverse health effects were associated with chronic exposure to higher concentrations of TSP and SO_2. Studies are plotted at the lowest concentrations at which increases were seen and by the reference numbers in the bibliography. The dashed lines correspond to the current National Ambient Air Quality Standards for annual mean concentration.

Table 23. Summary of evidence for health effects of chronic exposure to SO_2 and particulate matter.

Type of study	References	Effects observed	Annual average pollutant levels at which effects noted, $\mu g/m^3$	
			TSP	SO_2
Cross-sectional (four areas)	Lunn et al. (*56, 57*)	Increased frequency of respiratory symptoms; decreased lung function in five-year-olds	360	225
Cross-sectional study across Britain	Lambert and Reid (*61*)	Increased prevalence of respiratory symptoms	200	100
Cross-sectional (two areas)	Sawicki (*62*)	More chronic bronchitis, asthmatic disease in smokers; reduced FEV%	270	125
Cross-sectional (four areas)	Rudnik et al. (*63*)	Increased history and symptoms of respiratory illness	285	125
Longitudinal and cross-sectional	Ferris et al.	Higher rate of respiratory symptoms; and decreased lung function	180	55
Cross-sectional (two areas)	Hammer (*60*)	Increased frequency of acute lower respiratory disease	135	<25

Summary

The studies summarized in Table 22 indicate that increased mortality and morbidity are associated with exposure to 24-hr average TSP concentrations of 500-600 $\mu g/m^3$ and SO_2 concentrations of 300-400 $\mu g/m^3$ and a temporary decrease in lung function has been associated with a TSP concentration of 250 $\mu g/m^3$ and a SO_2 concentration of 300 $\mu g/m^3$. This conclusion is based on only two independent studies. There is little evidence concerning health effects of short term exposure to only one of these pollutants. Various studies not accepted in this assessment have reported health effects at lower pollutant concentrations, but we believe that the evidence from these studies is inconclusive.

The studies summarized in Table 23 indicate that increased morbidity is associated with chronic exposure to TSP concentrations exceeding 180 $\mu g/m^3$ (annual average). Though effects were found both with and without parallel increases in SO_2 concentration, there is no basis in these studies for evaluating the effects of elevated SO_2 concentrations without increased particulate pollution. Once again, one cited study (*80*) and several studies not accepted for this assessment have reported health effects at lower concentrations and with elevated SO_2 concentrations, particularly the studies in the CHESS program. In our opinion, the evidence for health effects at these lower concentrations is inconclusive, but should be the subject of continuing investigation. Though we have focused on the evidence from observational studies, the evidence from animal studies and controlled studies of human exposure must also be considered, particularly in relation to the less severe effects of short-term high exposures. These studies will also play an important role in future efforts to link health effects with chemical or size fractions of the SO_2-TSP pollution complex. Nonexperimental studies provide little information on this issue because of the collinearity of the components of interest. This will be especially important in studying fine particulates.

Although we have given single numbers as concentrations above which various health effects occur, these numbers are based on very sparse data from studies not designed to establish such values. Thus, the numbers are subject to uncertainty which is difficult to quantify.

In view of the limitations of studies based on multivariate analysis of data obtained from sources not oriented to air pollution research, future studies will be most informative if they involve thorough and detailed investigation of well defined populations.

Direct measurement and careful control of potential confounding factors will be especially important, as will improved measurement of the air pollution exposure of individuals. The need for such research may grow as energy usage patterns shift in response to limited availability of oil and natural gas.

The public health significance of this question is sufficient to justify the commitment of additional resources to improving the data base on health effects of sulfur oxides and particulate matter.

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Mathematical Models of the Uptake of Carbon Monoxide on Hemoglobin at Low Carbon Monoxide Levels

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Coburn's differential equation for the uptake of carbon monoxide by hemoglobin and two particular types of solution of this equation were considered and the solutions verified for a group of healthy adults consisting of 73 nonsmoking pedestrians or car passengers exposed to low levels of carbon monoxide as experienced in the city of Lyon. The CO levels at the breathing level and the walking speed of the subjects was continually measured, and the carboxyhemoglobin levels determined at the beginning and the end of each test journey. The values of all the other relevant parameters were also determined. The half-life of carboxyhemoglobin was studied as a function of the degree of activity, the age, the sex and the height of the subjects. Finally a mathematical model was set up to represent a periodic uptake of CO which made it possible to estimate the variations in the carboxyhemoglobin level for any subject during a period of a day or a week without any need to know the initial level.

There is normally a very small concentration of CO in the air as a result of natural phenomena, its level being between 0.01 and 1 ppm. Measurements carried out on the Isle of Sark (*1*), where motor vehicle traffic is prohibited, confirmed that the CO levels were always less than 1 ppm. Measurements made in urban areas in various places in the world over many years have resulted in a considerable quantity of information on CO levels. The exact location where the measurements are made is important, since the highest concentrations are found in the midst of a stream motor vehicles and also inside such vehicles, as confirmed by this investigation. Pedestrians walking along the sidewalks are exposed to a lesser concentration of CO than are motorists. People who are obliged to remain at certain critical locations such as toll booths, garages or in traffic jam in enclosed and poorly ventilated streets are exposed to high CO levels due to road traffic (*2,3*). In order to obtain some idea of the conditions, a person moving within a city will experience CO levels having an average level for the hour in excess of 30 ppm (*4*). American standards for permissible levels to which the public may be exposed are in fact sometimes exceeded (*5,6*).

Dangerous HbCO Level and Particularly Vulnerable Subjects

The effect of carbon monoxide is to reduce oxygenation of the tissues and this effect may be experienced immediately or after a longer period of time. Any increase above the endogenous level can in theory be harmful for a person having an extreme requirement for oxygen, and who cannot compensate a reduced supply of oxygen by physiological means. Such subjects consist mainly of people suffering from coronary atheromatic ischaemia or from cerebral vascular deficiencies. Also at risk

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here are people suffering from pernicious anaemia or from respiratory deficiencies, patients recovering from major surgery or premature babies. Aronow and Isbell (7) refers to a "critical" carboxyhemoglobin level of between 0.025 and 0.030 for angina pectoris sufferers, such a level giving rise to an appreciable reduction in the time elapsing before the onset of a painful attack following a given physical effort. The World Health Organization (5) estimates that the level for the population exposed to atmospheric pollution should not exceed these limits. In the case of our sample, the 0.025 level was exceeded for 19 out of the 73 subjects (pedestrians or car passengers) as a result of their displacement in the city. However this level can in theory easily be exceeded for subjects remaining in heavily polluted localities. The 0.025 carboxyhemoglobin level would result from an exposure to a 13 ppm CO concentration for more than 24 hr.

Kinetics of the Uptake and Elimination of Carbon Monoxide

Symbols and units used are summarized in Table 1. We used SI units, but for CO concentration used ppm because it is independent of the temperature.

Differential Equation

Coburn et al. (8) have proposed the following differential equation (1) for carboxyhemoglobin level as a function of time:

$$V_b\, M[O_2]/Pc_{O_2}\,(1/D_L + P_B - P_{H_2O}/\dot{V}_A)\, d[CO]/dt + [CO] = Pi_{CO}\, M[O_2]/Pc_{O_2} + \dot{V}_{CO}\, M[O_2]/Pc_{O_2}\,(1/D_L + P_B - P_{H_2O}/\dot{V}_A) \quad (1)$$

Numerical Values of the Different Parameters

The values given below are statistical averages for subjects in good health and very different values can apply in individual cases, particularly in the case of subjects suffering from certain diseases. The value of M can vary from 185 to more than 250, and we assumed a value of $M = 250$. $[O_2]$ was given a value such that: $[O_2] + [CO] + [X] = 8.92$ mmole/liter of blood (200 ml/l.) P_B was assumed to have a value of 99.3 kPa (745 mm Hg) for the town of Lyon, which is at an altitude of 120 m above sea level.

Pc_{O_2} and P_{H_2O} were assumed to have values of 13.3 kPa (100 mm Hg) and 6.3 kPa (47.5 mm Hg), respectively.

The value of P_{iCO} is directly related to that of C by the equation: $P_{iCO} = P_B \times 10^{-6}C$. We also assumed that $y = HbCO = 17\,[CO]/[Hb]$, (or $1000\,[CO]/1.316\,[Hb]$, if [CO] and [Hb] are in ml/100 ml and g/100 ml of blood, respectively), and similarly that $HbX = 17\,[X]/[Hb]$. The value of D_L is related to the height and body surface of the subject and the value decreases with age. A number of relationships have been proposed, and the resulting calculated values may differ 20 to 30% for the same subject. We used the following relationships (9):

For a man aged 18 or more:

$$D_L = 0.329H - 0.000135Y - 0.318$$

For a woman aged 18 or more:

$$D_L = 0.119H - 0.000087Y - 0.015$$

For a child:

$$D_L = 0.117A - 0.022$$

The value of V_b for adults depends on the sex of the subject and we assumed values of $m/13$ and $m/15$ for male and female subjects, respectively. For children we assumed values of $0.071m$, $0.075m$ and $0.080m$ for 15, 10 and 1-6 year old subjects respectively (10).

The value of $\dot{V}_{CO}$ for a standard male subject has been given as 5.2×10^{-6} mmole/sec (0.007 ml/min) (8). We assumed that the value varied with the total hemoglobin level $V_b[Hb]$ (for a standard male subject, $V_b = 5$ liters and [Hb] = 155 g/l. blood), giving:

$$\dot{V}_{CO} = 5.2 \times 10^{-6}\, V_b[Hb]/5(155)$$

The degree of alveolar ventilation is proportional (11) to the oxygen consumption $\dot{V}_A = 19.63V_{O2}$, and this consumption depends in turn on the power expended by the subject (12). Thus we have:

$$\dot{V}_A = 4.33 \times 10^{-2}\, P$$

Power Expended

The power expended is the sum of the basal metabolism, the muscular power and the specific dynamic action of the foods: $P = MB + PM + SDA$. The basal metabolism is proportional to the surface area of the body: $MB = Ax$.

Pandolf et al. (13) have established an equation giving the rate of energy expenditure for a subject when standing or when walking at different speeds and when carrying or not carrying a load.

$$P\,(SDA = 0) = 1.5m + 2(m + m')\,(m'/m)^2 + e(m + m')\,(1.5V^2 + 0.35\alpha V)$$

Table 1. Symbols and units used.

Symbol	Unit	Definition
A	m^2	Body surface area
$a(t)$		Other form of the coefficient in Coburn's equation
$b(t)$		Other form of the coefficient in Coburn's equation
C	ppm	Carbon monoxide concentration in air
[CO]	mmole/l. of blood	CO level in blood
d		A coefficient depending on the type of meal
D_L	mmole/sec/kPa	Pulmonary CO diffusion capacity
e		A coefficient depending on the condition of ground surface
$f(t)$		Function used for resolving Coburn's equation
$g(t)$		Function used for resolving Coburn's equation
H	m	Height of subject
[Hb]	g/l. of blood	Hemoglobin level
HbCO	fraction	Carboxyhemoglobin level with respect to the total hemoglobin
HbO_2	fraction	Oxyhemoglobin level with respect to the total hemoglobin
HbX	fraction	X hemoglobin level with respect to the total hemoglobin (e.g., nitrosylhemoglobin)
HEL	fraction	Limit endogeneous carboxyhemoglobin level with respect to the total haemoglobin
k	fraction/ppm	A constant for carboxyhemoglobin level
K	fraction/ppm/sec	Rate constant for carboxyhemoglobin formation
K_0	fraction	A coefficient employed in step-by-step calculation: carboxyhemoglobin and oxyhemoglobin levels
K_1	fraction/sec	Coefficient employed in step-by-step calculation: partial rate constant for CO uptake
K_2	fraction^2/sec	Coefficient employed in step-by-step calculation: partial rate constant for CO uptake
m	kg	Weight of subject
m'	kg	Load carried by subject
M		Haldane's constant
MB	W	Basal metabolism
(O_2)	mmole/l. of blood	Oxygen level in the pulmonary capillaries
p_i		Fraction of the daily energy allowance for one meal
P	W	Total power expended by the subject
P_B	kPa	Barometric pressure
P_{CO}^c	kPa	Average partial CO pressure in the pulmonary capillaries
$P_{O_2}^c$	kPa	Average partial oxygen pressure in the pulmonary capillaries
P_{H_2O}	kPa	Vapor pressure of water
P_{CO}^I	kPa	Partial CO pressure in inspired air
PM	W	Muscular power (expended)
sda	W	Instantaneous specific dynamic action per 1 kJ of food ingested at last meal
SDA	W	Specific dynamic action of foods
V	m/s	Walking speed
$\dot{V}_A$	mmole/sec	Alveolar ventilation rate
V_b	liters	Blood volume
$\dot{V}_{CO}$	mmole/sec	Rate of endogeneous CO production
V_{O_2}	mmole	Volume of oxygen consumed
κ_r	kJ/kg	Heat production to food/kg of body weight
ε	W/m^2	Basal metabolism per unit body surface area
[X]	mmole/l. of blood	Possible gas level other than O_2 and CO in the pulmonary capillaries (e.g. nitric derivatives)
Y	years	Age of subject
y	fraction	(= HbCO): proportion of carboxyhemoglobin with respect to total hemoglobin
$y(t)$		particular periodic solution of Coburn's equation
y_0	fraction	value of y at time t_0
y_{1m}	fraction	Initial measured value of HbCO
y_{2c}	fraction	Final calculated value of HbCO
y_{2m}	fraction	Final measured value of HbCO
α	per cent	Inclination
δ		Kronecker symbol (1 = standing, 0 = other cases)
τ	sec	Time constant
$\tau_{1/2}$	sec	Half-life

The validity of this equation has been verified for young male subjects of average height and weight (1.75 m, 78.2 kg). The equation gives the value of the total power expended, including the basal metabolism, but for a zero SDA value.

We also considered Scherrer's findings (*12*); he stated that the power expenditure amounts to 1.2 times the basal metabolism for a standing subject and to 1.1 times the same basal metabolism when the subject is sitting and at rest (and 0.9 times when the subject is asleep). We made use of a coefficient d to allow for these factors. Certain authors have shown that a female or an overweight subject expends less energy when at rest as a result of a smaller proportion of muscular tissue which accounts for the difference in metabolism with effort. The additional expenditure of energy as a result of performing work PM is the same (*14*). If we wish to apply the above equation for a subject of either sex then the first term ($1.5m$) in the expression must be a function of the sex. We accordingly replaced the first term by Adx, where x is a function of both age and sex (*15*) and the second term appears only for a stationary, standing subject. We then have:

$$P(\text{SDA} = 0) = Adx + 23(m + m')(m'/m)^2 + e(m + m')(1.5V^2 + 0.35\alpha V) \quad (1)$$

The SDA or additional postprandial heat is defined as the increase in the rate of energy expenditure resulting from the ingestion of a meal, the other conditions being basal. This specific dynamic action varies with time and it rises to a maximum value some 2 hr after the ingestion of a meal (*16*). Furthermore it should be noted that the SDA value depends on the type of food consumed and it can be assumed, as a first approximation, that it is a function of the energy value of the meal, this latter being a function of the age and sex of the subject. It is also proportional to the weight of the individual and we can accordingly refer to w_r, the heat allowance per kilo of weight of the subject. We therefore have:

$$\text{SDA} = mw_r(Y, \text{sex})p_r \text{ sda}$$

where sda is the SDA for 1 kJ of food and p_r is the fraction of the daily energy allowance for each meal.

What is the relative importance of MB, PM and SDA? With our mixed group of subjects made up half of pedestrians and half of car passengers we had values of $\overline{\text{MB}} = 91$, $\overline{\text{PM}} = 80$ and $\overline{\text{SDA}} = 23$. On considering a theoretical subject over a period of one week we obtained average values of MB, PM and SDA of 78, 13 and 17, respectively. Thus the SDA is approximately 20. It represents nearly a quarter of the basal metabolism to which we need to add the muscular work rate which can be greater than the basal metabolism. Thus the SDA is not negligible.

Solving the Differential Equation

Three methods of solving Coburn's equation are considered.

First Method: Step-by-Step Solution. Let y_1 and y_2 be the carboxyhemoglobin levels at times t_1 and t_2, respectively; if C remains unchanged from time t_1 to time t_2 we can write:

$$y_2 = y_1 + (t_2 - t_1)\left\{K_1 - [K_2/(K_0 - y_1)]\right\}$$

where

$$K_0 = \frac{17(8.92 - [\text{X}])}{[\text{Hb}]} \quad (1)$$

$$K_1 = \frac{17}{V_b[\text{Hb}]} \times \left[\frac{Pc_{O_2} + MP_B \times 10^{-6}C}{M\{(1/D_L) + [(P_B - P_{H_2O})/\dot{V}_A]\}} + \dot{V}_{CO}\right] \quad (2)$$

$$K_2 = \left(\frac{17}{[\text{Hb}]}\right)^2 \times \left[\frac{(8.92 - [\text{X}])Pc_{O_2}}{MV_b\{(1/D_L) + [(P_B - P_{H_2O})/\dot{V}_A]\}}\right] \quad (3)$$

The advantage of this method of solving the equation in comparison with the other two methods considered below is that no assumptions need to be made. The disadvantage is that an error is introduced, since no distinction is made between the tangent to the curve and the curve itself at each point.

Second Method: Analytical Solution. If we ignore [CO] (and [X] but it is not strictly necessary) with regard to $[O_2]$, then the basic equation can be put into the form of a linear first order differential equation:

$$(k/K)dy/dt + y = kC + \text{HEL} \quad (4)$$

This is also the form of equation proposed by Chovin and Richalet (*17*) except for the inclusion of

the HEL term, which was based on the results of the experimental investigation by Hanks and Farquhar (*18*). Peterson and Steward (*19*) have verified it for constant concentrations (50 to 200 ppm) in industrial conditions on the whole.

If, in addition, C can be regarded as a linear function of time ($C = at + C_1$) then the analytical solution to the equation becomes:

$$y = \mathrm{HEL} + K\{a\,[t - (k/K) + C_1\} + \{y_1 - k\,[a\,(k/K) - C_1] - \mathrm{HEL}\}\,e^{-Kt/k}$$

where

$$k = \frac{17 \times 8.92 M P_B \times 10^{-6}}{P c_{O_2}[\mathrm{Hb}]}$$

$$K = \frac{17 P_B \times 10^{-6}}{V_b[\mathrm{Hb}]\,[(1/D_L) + [(P_b - P_{H_2O})/\dot{V}_A]}$$

$$\mathrm{HEL} = \frac{17 \times 8.92 M \dot{V}_{CO}}{P c_{O_2}[\mathrm{Hb}]\,[(1/\dot{D}_L) + [(P_b - P_{H_2O})/\dot{V}_A]}$$

The time constant k/K is then given by:

$$\tau = \frac{8.92M}{P c_{O_2}}\,V_b\left(\frac{1}{D_L} + \frac{P_B - P_{H_2O}}{\dot{V}_A}\right)$$

The constant k is such that the HbCO level following an infinite time of exposure to a concentration C will be kC + HEL. In particular, the value of k is a function of the hemoglobin level and is independent of the level of activity. The value of the factor K, which defines the rate of uptake of CO by the hemoglobin, increases with the degree of alveolar ventilation and hence with physical activity. Standard values of k and K are listed in Table 3 below. The limit endogeneous carboxyhemoglobin level HEL also increases with the amount of physical activity, but the level remains very low ($\ll 0.002$).

This analytical method of solving the equation enables us to determine any HbCO level, if the initial level is known, provided the variation of C is linear and K remains constant during the interval concerned, which are not unreasonable assumptions.

Third Method: Periodic Solution. The two methods of solving the differential equation described above depend on a knowledge of the initial HbCO level. This well-established disadvantage can disappear if we ignore [CO] with regard to [O_2] and if the parameters K, C and HEL are periodic functions of time (k being constant for a given subject). It is possible to find a periodic solution by using some analytical properties. For convenience, we use a more mathematical language in this section. If we rewrite the equation

$$dy/dt + a(t)y = b(t)$$

with

$$a(t) = K(t)/k$$

$$b(t) = K(t)\,C(t) + K(t)\,\mathrm{HEL}(t)/k$$

this is a linear differential equation of the first order, whose general solution is

$$y(t) = y_0 f(t) + g(T)$$

with the new functions (*20*)

$$f(t) = \exp\{-\int_0^t a(u)du\} \quad f(0) = 1$$

and

$$g(t) = f(t)\int_0^t b(u)/f(u)\,du \quad g(0) = 0$$

If $a(t)$ and $b(t)$ are periodic functions of period T and if $a(t) \geq 0$, it may be easily shown that

$$\hat{y}(t) = g(t)f(t)/[1 - f(t)] + g(t)$$

is a particular solution which is periodic (of period T), and every general solution $y_0 f(t) + g(t)$ converges towards $\hat{y}(t)$ as t is increasing ($t \geq 3$ or $4T$) (*21*). Then the $\hat{y}(t)$ function is a convenient analytical tool to describe the actual variations of the carboxyhemoglobin level $y(t)$ if the data used K,C,HEL are periodic functions of time. So we make the realistic assumption that these data representative of the activity and CO exposure of a person are periodic over a period of 24 hr, or, better, over 7 days; moreover, since these variations are known, it is no longer necessary to measure or to choose arbitrarily the initial HbCO level to describe the variations of the HbCO level in any time interval. In practice, we obtain the values of K, HEL and C every 15 min (during 24 hr or 7 days) and calculate the basal integrals $f(t)$, $g(t)$ at the same moments by numerical methods on a computer.

For the second and third methods, we ignore [CO] with regard to $[O_2]$: the greater the value for HbCO, the more k and HEL are overestimated. We can give $[O_2]$ its initial value $[8.92 - (Hb/17)\ y_1]$ or its mean value. Besides, if we do not ignore [X] when we can estimate it, we must replace 8.92 by 8.92 – [X].

Experimental Verification

In order to validate the theoretical analysis, we carried out tests with a total of 73 subjects whose ages varied from 18 to 60 years and who all stated that they were nonsmokers. This sample was divided into two groups of subjects: one group consisting of car passengers who remained seated in each case for the duration of a test journey within and around the town, and a second group consisting of pedestrians who walked at a nearly constant speed in each case in the actual polluted atmosphere existing in certain streets of the city of Lyon. The pedestrians were accompanied by a technician who ensured that the walking speed was maintained throughout each test journey on making measurements at intervals of 3 to 4 min (the mean speed is 1.09 m/sec).

Samples of blood were taken at the beginning and end of each journey and these samples analyzed in order to obtain values of [Hb], y_{1m} and y_{2m}. The analysis of the blood samples was based on the method developed by Boudene, Godin and Roussel (*22*), where the proportions of hemoglobin and CO in the blood were determined by means of infrared spectroscopy. The carbon monoxide levels in the atmosphere were measured on a continuous basis by means of a polarography technique by using a portable Ecolyser and a paper recorder.

For each of the subjects we had in addition to our knowledge of the values of [Hb], y_{1m}, y_{2m} and C, information concerning the sex, weight, height and age of the subject, the load carried by the subject, the time of day when the subject undertook the test journey and continuous information on the walking

Table 2. Average values of the different parameters for the sample subjects.

Parameter	Men	Women
n	37	36
Age	32	32
[Hb], g/l	147	133
m, kg	71	57
m', kg	3	3
H, m	1.75	1.62
C, ppm	13.9	13.7
V, m/sec	0.70	0.64
Duration, min	126	123
D_L, mmole/sec/kPa	0.190	0.175
A, m²	1.85	1.59
V_b, liters	5.46	3.78
$V_{CO} \times 10^{-6}$, mmole/sec	5.55	3.49
y_{1m}	0.019	0.018
$\sigma_{y_{1m}}$	0.007	0.006
y_{2m}	0.023	0.021
$\sigma_{y_{2m}}$	0.008	0.006
τ_w, min		
Activity A	236	208
Activity B	140	117

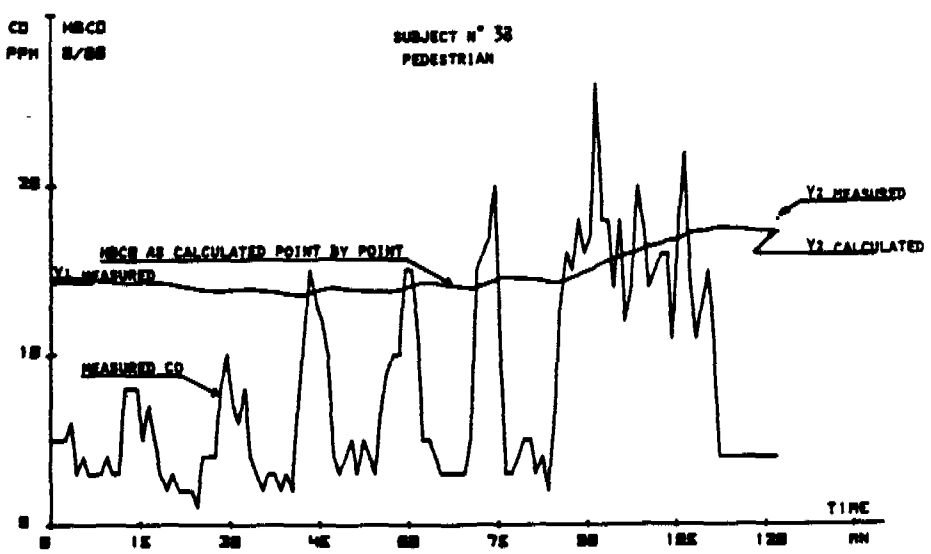

FIGURE 1. Example of an experimental validation of analytical solution.

speed of the pedestrians. Knowing the initial level in each case we calculated the successive carboxyhemoglobin levels throughout the duration of the test and the final level y_{2c} for each subject. An example of the results obtained as a result of making these calculations is given in Figure 1. The calculations were made on using the analytical method without approximate rectification of $[O_2]$ to solve the differential equation and also on using the step by step method on estimating HbX = O or HbX = 0.010. In Table 2 we list with respect to the sex of the subjects, average values of the different parameters for the sample subjects: age, [Hb], m, m', H, CO concentration, V, duration of the tests, D_L, A, V_b, $\dot{V}_CO$, y_{1m}, y_{2m} and the half-life $\tau_{1/2}$ for the subjects when at rest (A) and when walking at a speed of 4 km/hr (B).

As a verification of the validity of the theoretical calculations we compared the final measured levels with the different calculated values. We applied statistical tests to the pairs of values (y_{1m}, y_{2m}), (y_{2m}, y_{2c}) and (y_{2m}/y_{1m}, y_{2c}/y_{1m}) in order to ascertain if there were any significant differences between them (at 5%) for different subsamples as regards the sex and the type of activity. As a result of this it was found that the initial and final measured levels y_{1m} and y_{2m} were significantly different ($p = 10^{-7}$). The method of calculation employed did not have any effect on the results; the differences in the levels determined by each method were not significantly different from one another. There was no significant difference between the calculated and measured levels either for the whole sample of subjects or, except for the case of male pedestrians, for any subsample. This was found for both the (y_{2m}, y_{2c}) and the (y_{2m}/y_{1m}, y_{2c}/y_{1m}) pairs of values. We calculated also $\Delta = [\text{sign of}(y_{2m} - y_{1m})](y_{2c} - y_{2m})/y_{1m}$, which is positive when the calculated change is too great. Mean Δ showed that the calculated changes were generally lightly too small and in the case of male pedestrians clearly too small.

The calculated results as a whole were very satisfactory for all subjects and particularly so in the case of female pedestrians. Thus we can conclude that the two method (analytical or step-by-step solutions) were equally valid, at least when the level of HbX + HbCO is low. The analytical solution is therefore to be preferred for environmental pollution since it is easier to use; we can give if necessary to $[O_2]$ its initial or mean value. The differential equation for the uptake-elimination of carbon monoxide by hemoglobin and the use of the selected parameter values to model the phenomena is generally valid, although it would appear that the changes in the HbCO levels are underestimated for male pedestrians (the degree of alveolar ventilation is no doubt insufficient in the model).

Applications

Effects on a Particular Subject

The procedure employed to verify the validity of the theoretical approach can also be applied to real life cases. This requires measuring or estimating the CO concentrations throughout the period of time being considered and assuming an initial HbCO level. We can then determine the effects of the changing environment on a real or imaginary subject.

However, it is often difficult, if not impossible, to obtain information on the CO concentration in the air and on the level of activity of the subject at each instant. We must therefore ask what error would be introduced on using average values of CO concentration and/or of the level of activity of the subject? To answer this question let us consider a female subject exposed to an average CO concentration of 15 ppm and walking along at an average speed of 1 m/sec, with both these values varying from zero to twice the average level. The initial level of HbCO is assumed to amount to either 0.010 or 0.050. When calculating the results for this case it was found that no errors are introduced when assuming these average values despite the random variations in the instantaneous values of CO concentration and the level of the subject's activity. In general it was found that only a small error is introduced by assuming an average value for the level of activity but that a significant error can result when assuming an average value for the CO concentration and the period of integration involved is greater than the half-life (see below). The error, however, becomes negligible for periods of integration which are less than the half-life by an order of magnitude or more.

Graphs for Determining the Uptake and Elimination of CO Under Different Conditions

A desk calculator has to be employed to obtain analytical solutions of the differential equation, and we have therefore produced a series of graphs resulting from theoretical calculations which show the way in which CO is taken up or eliminated from hemoglobin for CO concentrations of 0, 10, 30, 50

and 100 ppm for an average (French) women (1.60 m high, 55 kg in weight):

Level of activity A: Subject seated and at rest. $\dot{V}_A$ = 4.06 mmole/ sec = 5460 ml/min

Level of activity B: Subject walking along at a speed of 4 km/hr. $\dot{V}_A$ = 8.87 mmole/sec = (11930 ml/min)

Level of activity C: Subject involved in some strenuous physical or sporting activity such as cycling (at a speed of 15 to 20 km/hr), football or swimming, resulting in a doubling in the value of $\dot{V}_A$ compared to the value for activity B: $\dot{V}_A$ = 17.74 mmole/sec = 23860 ml/min

Two sets of curves are shown on each of these graphs for the different CO concentrations and levels of activity, one set originating from a zero and the other set from a 0.100 HbCO level.

Reference can be made to this graph in determining the approximate fixation-elimination of CO for a subject for a given initial level of HbCO and for continuously varying concentrations of CO in the atmosphere and of levels of activity of the subject. The graphs include curves for each of the three levels of activity for each of the CO concentrations. As an example of the use of these graphs we can consider (see Fig. 2) the case of an average female subject having an initial HbCO level of 0.020 who is successively exposed to different CO concentrations as follows: 30 ppm for 1 hr while at rest, HbCO = 0.028; 50 ppm for 1 hr while walking along at a speed of 4 km/hr, HbCO = 0.049; 0 ppm for 1.5 hr while at rest, HbCO = 0.037; 100 ppm for 1 hr while at rest. On referring to the appropriate graphs for these exposures it will be found that the final HbCO level for the subject amounts to 0.067.

Model of Periodic Conditions

Ott and Mage (*23*) used a simplified point-by-point determination of the HbCO level, CO concen-

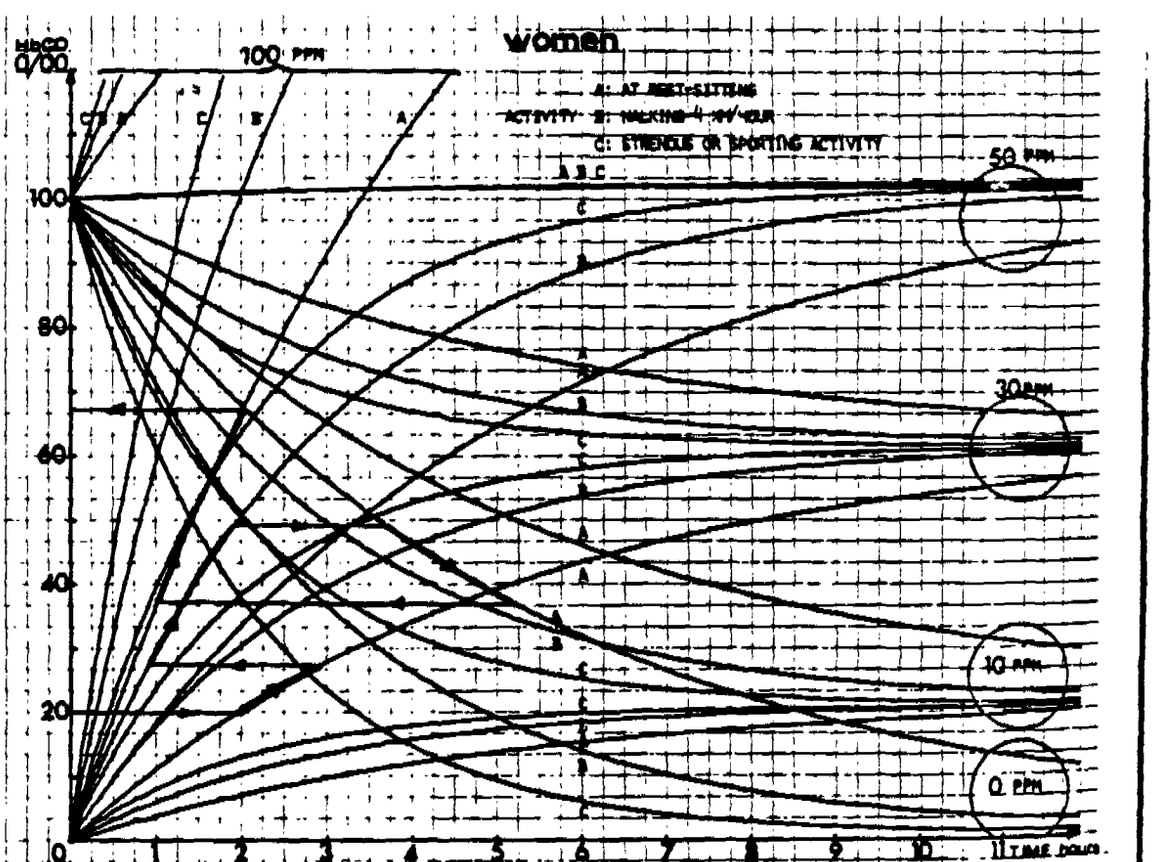

FIGURE 2. Graphs of the uptake-elimination of CO for an average woman, with constant concentration and activity and example of use.

tration being known hour by hour and the physical activity being constant. For a more precise calculation, a point-by-point determination is only possible in the case of relatively short periods of time. For longer periods of time and in cases where the CO concentrations and the levels of activity of the subject vary in a periodic manner it is better if we make use of the periodic method of solving the differential equation. We employed this method for solving the differential equation for two different cases, the time base being a quarter of an hour and the most significant period for the calculations being 1 week. The details of these two cases and the results of the calculations were as follows.

First Case. A customs officer whose place of work was at the side of the road near the French-Swiss frontier lived in the surrounding countryside. The CO concentration at the place of work was measured during the winter of 1978. It was found that the carboxyhemoglobin level varied from 0.002 to 0.033. The level exceeded 0.025 for 3.3% of the total time (corresponding to 14% of the working time) and the average CO concentration (working and rest periods combined) amounted to 3.7 ppm.

Second Case. A saleswoman lived on the outskirts of a large town and worked in a shop located in the main street and in the vicinity of road traffic from Tuesday to Saturday. She travelled to work by bus and spent a part of the weekend in the country. The CO concentrations taken into account were those actually measured at the side-walk of the main street. The CO concentrations in the other locations and the levels of activity taken into account were as estimated. On assuming the subject to be a nonsmoker, it was found that the HbCO level oscillated between values of 0.002 and 0.022. The average CO concentration amounted to 4.7 ppm (Fig. 3).

In order to have some idea of the effects of pollution due to motor vehicle traffic in comparison with the effects of smoking cigarettes (assuming 10 inhalations of 30 ml at 4% CO concentration per

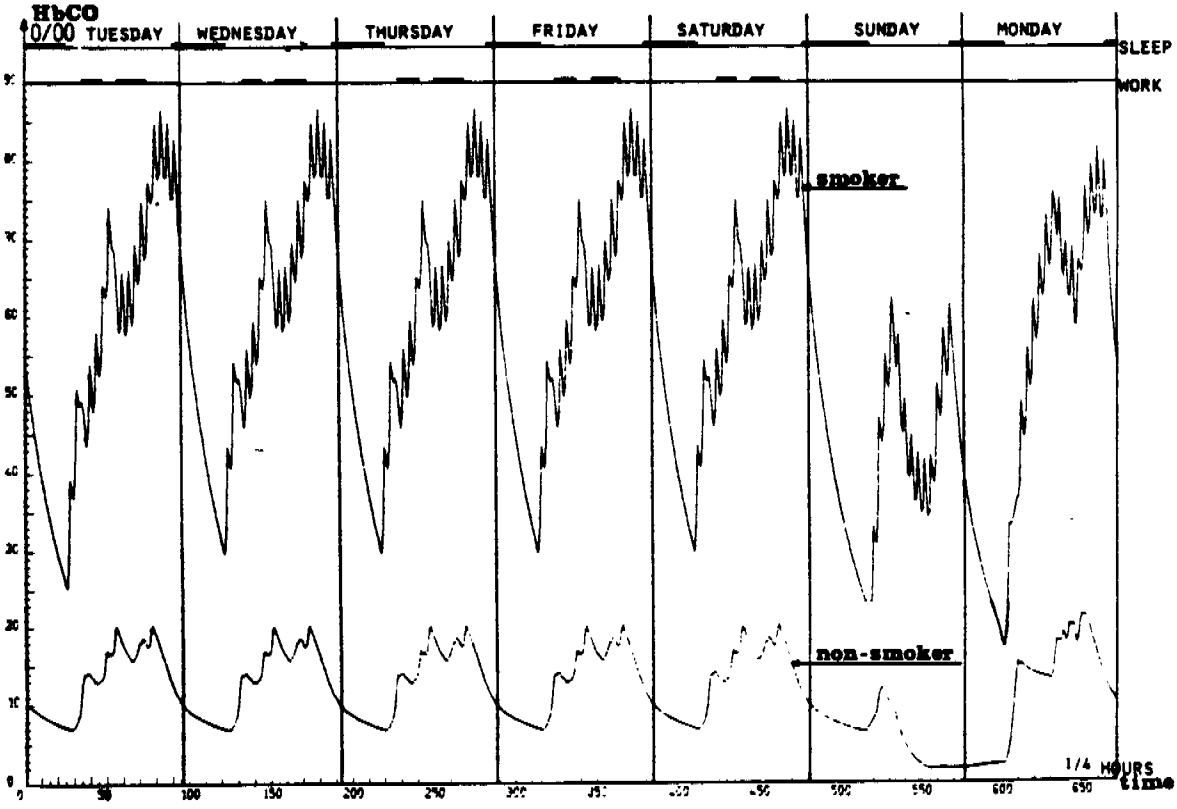

FIGURE 3. Simulation of the periodic variation in HbCO level for a nonsmoking saleswoman and for a subject smoking a total of 103 cigarettes per week.

cigarette) we also considered the case of the same saleswoman smoking at the rate of one cigarette per hour (103 cigarettes per week). The results of the calculations for this case are also shown on Figure 3. The HbCO level oscillated between values of 0.017 and 0.087, while the average CO concentration due to both the motor vehicle traffic and the smoking amounted to 18.3 ppm. The HbCO level exceeded 0.025 for 97% and 0.040 for 79% of the time. The levels were in general some four times greater for the cigarette smoking than for the nonsmoking subject.

The simulation of periodic variations in carboxyhemoglobin levels would appear to be a very useful technique in assessing the effects of carbon monoxide pollution of the atmosphere and of the variations in the actual CO concentration. The calculated HbCO levels given in the examples above are quite consistent with the HbCO levels quoted in the literature (*24-28*). It is necessary, however, to have information on the behavior of the subject on a quarter of an hour to quarter of an hour basis, but there are no problems in making assumptions concerning the behavior of a subject over certain very long periods of time (nighttime and rest periods). It is accordingly possible to determine the effects of any particular variations in CO concentrations during specific periods of time (e.g., during working hours or when travelling). Thus this technique has many potential applications.

Half-life of the Carboxyhemoglobin

Given a constant CO concentration in the air, the time involved for the HbCO level to change from level y_1 to level y_2 is given by:

$$\Delta t = -\tau \log \frac{y_1 - \text{HEL} - kC}{y_2 - \text{HEL} - kC}$$

If the atmosphere is unpolluted ($C = 0$) then Δt is the period of time during which the HbCO level decreases from y_1 to y_2. Thus we can determine, for example, the time needed for the HbCO level to fall from 0.200 to 0.010 and from 0.50 to 0.10 for the three standard subjects (male, female and child) and for the previously defined levels of activity A, B and C (Table 3).

If we neglect HEL in the equation for the value of Δt (HEL is always small and is a function of the level of activity of the subject), it then becomes a simple matter to determine the periods of time for the initial HbCO levels to be halved. The times Δt are then independent of the initial and final HbCO levels, and they depend only on the levels of activity of the subjects and the physiological factors involved. Thus we can determine the half-life ($\tau_{1/2} = \tau \log 2$) in each case, this being the period of time for the HbCO level to fall to half of any given value in an unpolluted atmosphere (Table 3). The real half-life is a little lower because we ignore [CO] with regard to [O_2].

The lower the value of $\tau_{1/2}$, the faster will any HbCO level be reduced to one half in an unpolluted atmosphere, and conversely the faster will the new level be doubled in the case of a constant concentration of CO, given that Δt is proportional to τ for such changes in level. The time taken for the HbCO level to double will in fact be proportional to τ (or to $\tau_{1/2}$) the value of this time constant in turn depending essentially on the value of y_2 with respect to the absolute maximum level kC. Thus it would be important to have a good knowledge of half-life. It is interesting to consider what are the population groups (healthy subjects) that are most sensitive to CO pollution in terms of half-life values. The results of the calculations for our sample subjects showed that the standard deviation for the half-life values for either sex amounted to 8%. Thus calculated individual half-life values will deviate appreciable

Table 3. "Standard" values, for 30 year-old men and women and for 6 years-old children, of the constant k, the alveolar ventilation rate $\dot{V}_A$, the rate constant for HbCO formation K, the half-life, the time need for the HbCO level to fall from 0.200 to 0.010 and from 0.050 to 0.010 in unpolluted air, for the levels of physical activity A (at rest-sitting), B (walking 4 km/hour) and C (strenuous or sporting activity).

	Men, k = 0.00183/ppm			Women, k = 0.00202/ppm			Children, k = 0.00223 ppm		
	Activity level A	Activity level B	Activity level C	Activity level A	Activity level B	Activity level C	Activity level A	Activity level B	Activity level C
$\dot{V}_A$, mmole/sec	5.17	10.88	21.77	4.06	8.87	17.74	3.23	5.12	10.25
$K \times 10^{-7}$, fraction/ppm/sec	0.95	1.61	2.35	1.11	1.91	2.75	1.69	2.15	2.81
Half-life $\tau_{1/2}$, min	223	131	90	210	122	85	152	120	92
τ (0.20 → 0.01), min	1030	587	402	973	546	379	706	535	410
τ (0.05 → 0.01), min	575	321	220	543	299	207	494	293	[illegible]

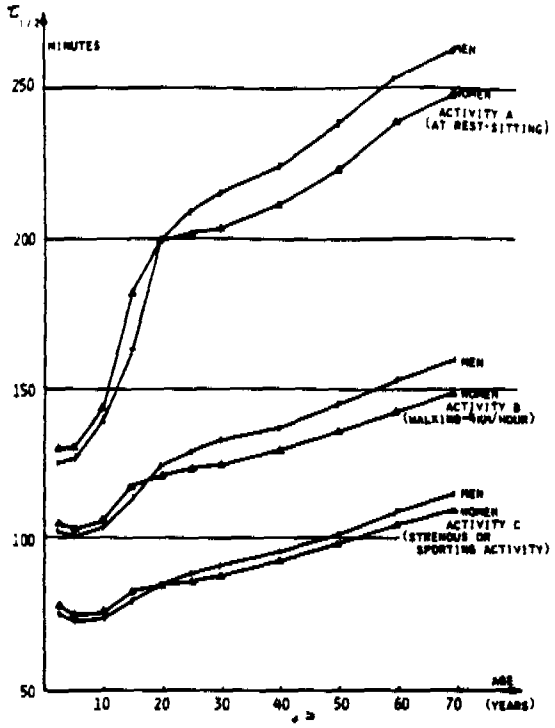

FIGURE 4. Effects of age and the level of physical activity on HbCO half-life.

from the average and the actual deviation will be even greater in the case of the actual population.

The half-life increases with age, the increase being rapid up to the age of 20 years, after which the increase with age slows down (Fig. 4). Age has a greater effect on the half-life than does the sex of the subject. Thus it may be seen from Figure 4 that the half-life for subjects at rest doubles as the age increases from 2 to 70 years, whereas the difference in half-life between male and female subjects does not exceed 6%. The half-life decreases with physical activity, the effect here being about the same for both male and female subjects but less pronounced for children where the muscular power expended is a small proportion of the total power expended. The degree of variation in the half-life with age or the sex of the subject decreases as the level of activity increases. We also studied the effect of the height on the half-life in the case of healthy subjects whose weight was an optimum with respect to height according to the relationship: $m = 75H + 0.25Y - 67.5$ for a male subject, the weight being assumed to be 5 to 10% less for a female (*29*). Height had only a slight effect on half-life in the case of female subjects involved in a low level of activity, when $\tau_{1/2}$ was found to increase with height.

Conclusions

The uptake-elimination of carbon monoxide by hemoglobin, i.e., the variation in the level of carboxyhemoglobin (HbCO) of a subject, can be defined by a fairly complex differential equation which involves a number of physiological parameters. We verified the validity of this equation on a sample of 73 subjects made up of persons of both sexes, and for different levels of physical activity and low carbon monoxide levels. As a result of our tests on these sample subjects we established the validity of two methods of simulating the uptake-elimination of carbon monoxide which take account of the nonpathologic variations for individual subjects. Thus the HbCO levels at each instant of a given period of time (day, week, etc.) can be predicted with reference to initial level and on taking account of the applicable conditions as a result of an analytical method of solving the differential equation (actual calculations in each case or use of an existing set of graphs based on previous calculations). This can be done better by a mathematically based simulation of the periodic variations in HbCO levels without reference to initial level. The HbCO levels depend first of all on the CO concentration in the atmosphere and then on the level of physical activity, the age (the half-life increasing with age) and finally on the sex (the half-life is a little shorter for the female sex) of the subject.

It would appear that the HbCO levels predicted by the periodic simulation are a function of the HbCO half-life (as determined by a fairly simple calculation) but this matter should be the subject of a more systematic statistically based study.

Although we did not study the matter in any detail, it appears that subjects suffering from certain ailments and in particular from respiratory deficiencies for whom certain physiological variables deviate appreciable from the normal values can have carboxyhemoglobin levels that are significantly different from those encountered in the course of this investigation. We need more detailed information for such cases.

It is difficult to reach any conclusion with regard to the short-term and long-term effects of the low carboxyhemoglobin levels that have been observed in a nonsmoking population. With the exception of people who are exposed to the atmospheric pollution due to road vehicle traffic, in particular because of their occupation, it appears however that there are no effects on either the alertness or sensory perception of pedestrians or car passengers making journeys of short duration in the city of Lyon. For the car passengers in our sample, who

were the subjects exposed to the highest level of atmospheric pollution, the HbCO level amounted to 0.027, on the average, at the end of their test journey. The levels of atmospheric pollution normally encountered can however have effects on advent of arteriosclerotic lesions. Thus such levels are sufficient to result in the occurrence or an increase in the seriousness of acute ischaemic incidents in subjects who already suffer from artery deficiencies.

Apart from being useful in establishing carbon monoxide atmospheric pollution indices, the results of this study may also contribute to the establishment of the standards for acceptable carbon monoxide concentrations on the basis of the following approach: establish the carboxyhemoglobin levels that must not be exceeded for both healthy and pathological subjects; determine the CO concentrations that are in agreement with these carboxyhemoglobin levels by simulating the cyclic variations as well as employing other techniques.

In making this approach, it must be understood that there is no such thing as a population of average subjects, but the physiological characteristics and hence the sensitivity to the effects of carbon monoxide vary in accordance with a Gaussian distribution about the mean values that we have considered here for healthy subjects. There is also the fact that there are pathological variations of physiological data for a significant proportion of the population.

More generally, the results of the study can be of use whenever it appears to be necessary to give proper attention to certain periods of time that are being studied out of their normal context (e.g., in the case of industrial medicine studies periods of time, other than the concerned with work high carbon monoxide concentration considered periods, could affect carboxyhemoglobin levels), first for low pollution, because the precision of certain methods is a good as low is HbCO level.

This study has been the subject of an internal report (*30*).

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Noise and Stress: A Comprehensive Approach

by Jack C. Westman* and James R. Walters†

The fundamental purposes of hearing are to alert and to warn. As a result sound directly evokes emotions and actions. The processing of sound by the brain is outlined to provide a biological and psychological basis for understanding the way in which sound can become a human stressor. The auditory orienting response, startle reflex and defensive response translate sound stimuli into action and sometimes into stress induced bodily changes through "fight or flight" neural mechanisms. The literature on the health and mental health effects of noise then is reviewed in the context of an integrated model that offers a holistic approach to noise research and public policy formulation. The thesis of this paper is that research upon, and efforts to prevent or minimize the harmful effects of noise have suffered from the lack of a full appreciation of the ways in which humans process and react to sound.

Introduction

The damaging effects of noise usually are regarded as limited to the structures of the ear through impairing one's ability to hear sounds such as speech and music. Often unappreciated is the fact that noise has more pervasive physiological effects (*1*, *2*).

In the course of evolution, certain fishes developed organs of hearing to orient themselves in space. In amphibians, vision provided the ability to locate prey but was not sufficient in terrestial environments to warn of other predators. Hearing accordingly developed as an organ for perceiving and responding to danger (*3*). Hearing also has played a role in sexual mating behaviors in mammals and even insects. These primitive functions exist in humans as well.

From the outset sound has evoked emotions and actions through the inner ear's direct connections to "fight or flight" neural mechanisms via the autonomic nervous system. Because of this defensive purpose, hearing also cannot be turned off, and sound registers in the brain even during sleep. Only later in primate evolution did the auditory system include higher cerebral centers permitting the appearance of spoken language.

The current usage of the terms "nonauditory" or "extraauditory" is unfortunate. This distinction designates as nonauditory the auditory system's original, primitive influence upon wakefulness and body activity. The auditory system and physiological responses to sound are inseparably connected. Therefore, all of the effects of noise on the body mediated by the ears are "auditory" effects. More precisely, the effects of sound on the body through vibration of structures other than those of the auditory system are "non-auditory" or "extra-auditory."

Another basic consideration in understanding the functioning of the auditory system merits emphasis. The human auditory system was designed to process the frequencies and intensities relevant to survival in the sound environments of nature. The evolutionary process has not allowed humans enough time to adapt hearing to sounds generated by loud modern noise sources. This means that the auditory apparatus is not prepared to cope with commonly encountered urban and industrial noise. Consequently, we find ourselves exposed to sound envi-

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ronments that overload the auditory system. An analogous situation would occur in the visual system if we were forced to look at the sun and thereby damage the retina.

The fundamental relationships of hearing to emotion and action and the auditory system's vulnerability to modern sounds are not appreciated sufficiently by the public. Research also has suffered from a lack of breadth and depth in conception resulting in contradictory findings. For example, laboratory studies of healthy young people have concluded that noise has no harmful psychophysiological effects on humans. At the other extreme are reports that jet aircraft noise increases psychiatric hospital admissions.

We lack a comprehensive model to ensure that research on sound includes the critical variables that make it a significant source of human stress. Much of the research cited in this paper suffers from methodological inadequacies because noise is but one of a number of variables affecting complex human beings. Before delineating the system levels involved in bodily responses to sound, we first will outline the neuroanatomy and physiology of the central processing mechanism of sound.

Neuroanatomy of the Auditory System

An appreciation of the structural basis for physiological and behavioral responses to sound can be gained from knowledge of the neuroanatomy of the auditory system (Fig. 1). The auditory pathways of the central nervous system consist of direct pathways from the inner ear to the auditory cortex and indirect pathways to the reticular activating system which connect to the limbic system and other parts of the brain, the autonomic nervous system and the neuroendocrine system (4).

The direct auditory connections consist of ascending pathways which carry impulses excited by sounds from the receptor cells in the organ of Corti to the auditory centers in the cerebral cortex. These pathways end in the temporal lobe where the sum of incoming impulses are consciously perceived and interpreted. The ascending auditory pathways travel along the auditory nerve via the cochlear nucleus, superior olivary complex, inferior colliculus, nuclei of the lateral lemniscus and geniculate body to a number of areas in the auditory cortex which in turn are connected to other cortical areas that

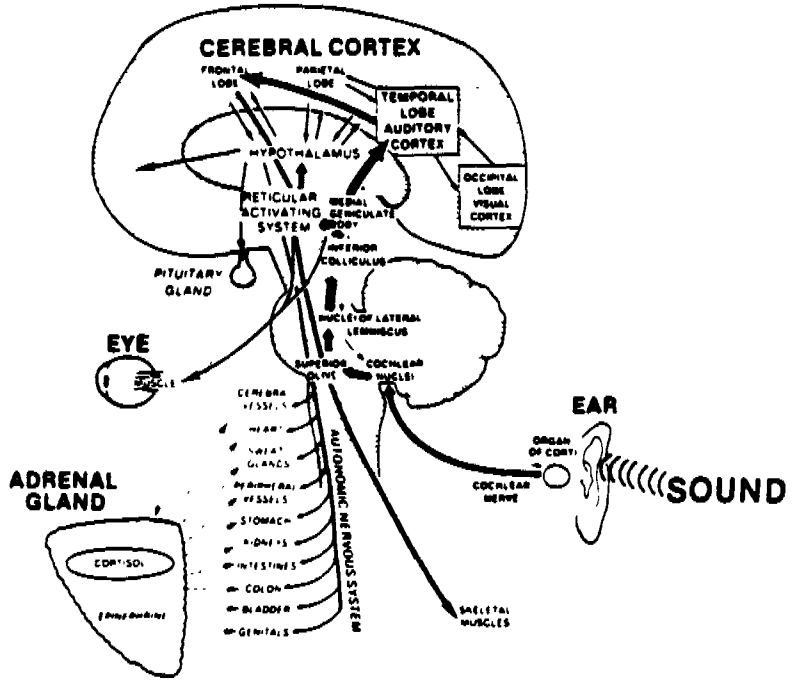

FIGURE 1. Processing of sound by the brain.

receive inputs from the other sensory organs as well.

There also are descending pathways from the temporal cerebral cortex to the dorsal cochlear nucleus via the inferior colliculus and to the organ of Corti via the medial geniculate body, inferior colliculus and lateral lemniscus through the olivocochlear bundle. These descending pathways have inhibitory and, to a minor degree, excitatory influences.

In addition to these direct pathways to and from cerebral cortex, there are a variety of indirect connections from the inner ear to the brain centers that control basic physiological, emotional and behavioral responses of the body. Nerve fibers branch out from the various synaptic junctions along the direct auditory pathways to motor cell nuclei subserving reflexes within the brainstem and to the reticular activating system in the midbrain.

Impulses reaching the reticular activating system excite still other impulses that spread to higher cerebral centers that control alertness, cognition and motor performance. At the same time the reticular activating system conveys impulses to hypothalamic autonomic nervous system centers which are linked to the sympathetic-adrenal neuroendocrine system and thereby regulate the secretion of the catecholamines, adrenaline (epinephrine) and noradrenaline (norepinephrine). Impulses conveyed by the reticular activating system also are transmitted to the pituitary-adrenal neuroendocrine system which secretes corticosteroids (cortisol). The catecholamines play an important role in mobilizing immediate adaptive resources of the body, and the corticosteroids provide for more enduring adaptation to prolonged stress (*5*). Thus, the auditory apparatus is connected to the entire central nervous system and the neuroendocrine system as well.

Physiology of Sound

In conjunction with the other special senses, the auditory system serves to maintain the arousal of the brain projections to the temporal cortex and the reticular activating system via the limbic system and the hypothalamus. In this way cognitive processes and emotions interplay with sound stimuli in influencing the state of consciousness.

The cerebral cortex requires a certain level of arousal to make optimum use of incoming sensory information upon which efficient behavior and physiological functioning depend (*6*). Neither underarousal nor overarousal is conducive to effective performance of physiological functioning (*7*). Sound can improve performance on tasks which are inherently underarousing, repetitive, and monotonous. Conversely, sound can impair performance on tasks demanding concentration and complicated responses (*8*). Sound contributes to the homeostasis of the central nervous system and consequently influences the physiological homeostasis of the body through the autonomic and neuroendocrine centers of the hypothalamus.

The arousal level of the central nervous system depends upon the intensity, complexity, variability, predictability and meaning of sound stimuli. The auditory system responds most to changes in the timing of sound stimuli. Therefore, a transient increase in the firing of auditory neurons may be produced by the termination of a sound as well as by its inception. Some neurons in the auditory system respond to stimulus onset with a high rate of impulse discharge, quickly cease firing, remain silent while the stimulus is continued, and discharge a second burst of impulses when the stimulus stops. However, in a much larger number of neurons, the rate of firing declines to a lower level of activity shortly after the initial high frequency discharge and then is tonically maintained during long periods of continued stimulation. These sound stimulus-induced alterations persist after the stimulation ceases (*9*).

The direct effects of certain sounds on emotions and attitudes is illustrated by the fact that chalk scraping on a blackboard can cause chill sensations in a listener. Musical rhythm, tempo and melody can evoke moods ranging from calmness to excitation or elation. Music also can promote positive attitudes toward work. The further influence of higher cerebral cortical centers on the emotional reaction to sound stimuli is illustrated by a study of sound in hospitals in which one source of annoyance was staff conversations in the halls, not because of undue loudness but because of the discussion of patients (*10*).

Sound stimuli also influence the other sensory systems. For example, sound input overload can induce visual changes in color perception, cause nystagmus and vertigo and even act as an analgesic (*11*).

In summary, sound stimuli play a vital role in maintaining arousal of the brain and thereby influence the basic physiological functioning of the body. Sound may influence the body after cessation of the stimulus through reverberating neural circuits within lower and higher brain centers. In this way sound can produce physiological reactions that develop a momentum of their own independent of the original stimulus.

Fundamental Auditory Responses

Orienting Response (Novelty Reflex)

The basic behavioral response to all sound stimuli is the orientation reflex, which involves ascending and descending auditory cortical pathways and is reflected by an arousal pattern in the electroencephalogram. The response orients the head and eyes toward the source of a sound in order to ready the organism to receive and respond to the sound stimulus situation. There is an associated decrease in auditory threshold and increased attention to the sound stimulus.

The orienting response occurs to sounds of low or moderate intensity and significance. The person's cognitive appraisal of the sound stimulus determines the intensity and duration of the orienting response. It extinguishes, or habituates, after varying repetitions so that the individual can accommodate to familiar and insignificant sounds with relative ease and concentrate on a preferred activity. If an appreciable amount of time passes between repetitions of a specific sound, habituation disappears and repetition of the same sound again evokes an orientation response. Habituation usually does not occur if attention to a sound is voluntarily sustained or if a sound has special significance, either positive or negative. Sounds of close to hearing threshold intensity do not easily habituate, probably because of the auditory system's difficulty in assessing their significance.

Even after behavioral habituation has occurred, sound stimuli continue to activate both cortical and subcortical areas of the brain (*9*). This is in part because excitation transmitted by the reticular activating system continues to arrive in the cerebral cortex after that transmission directly ceases. When the decision is made not to orient to a sound, descending cortical excitation actively restrains, but does not eliminate, the reticular activating system's excitation from spreading to higher areas of the brain. After the orienting response to sound habituates, there may be no change or an increase in the amplitude of the electrical responses evoked in the cerebral cortex and the medial geniculate body. The reticular activating system and the structures that it influences continue to be affected by sound even after behavioral habituation has occurred. This is not surprising because the organism's survival would be threatened by decreased alertness to danger if unattended stimuli were excluded from cognitive appraisal.

Startle Reflex

The second basic auditory response is the startle reflex which is evoked by sounds of sudden, intense, or frightening significance. The reflex has a series of components. First, the middle ear muscle reflexes via the superior olive to the tensor tympani through the fifth cranial nerve and to the stapedius muscle through the seventh cranial nerve provide a small degree of protection against sounds of extremely high intensity. The auropalpebral reflex via the superior olive and the sixth cranial nerve produces eye blinking. There also is opening of the mouth and flexion of the neck via the seventh and eleventh cranial nerves. More generally, there is flexion of most muscle groups in a "freezing" posture with raising of the shoulders, abduction of the arms, flexion of the fingers, contraction of the abdomen, and bending of the knees mediated by the ascending auditory and descending cerebral cortical motor pathways. The typical reflex is completed in less than one second.

Those components of the startle reflex that reflect cerebral cortex activity are subject to habituation or enhancement, however, those involving lower centers in the brainstem are not. The startle reflex accordingly can be decreased by anticipation, increased by background sound levels and exaggerated by emotional states such as fear.

The Defensive Response ("N" Response)

Although usually an extension of the orienting or startle responses, the defensive response merits separate consideration because it can occur independently of them and does not require sounds of high intensity. This response is produced by sounds of sufficient intensity, significance or duration to be perceived as threatening and to mobilize a "fight or flight" reaction. The response includes alerting of the cerebral cortex, emotional arousal, and preparation of the body for action (*12*).

Sounds in the range of 70 to 120 dB can produce the defensive response which appears first in the form of skeletal muscle tension that quickly reaches its peak and decays within a few seconds. Next there is a decrease in skin electrogalvanic resistance which changes more gradually than the skeletal muscle tension. Pupillary dilation occurs as well. A variety of circulatory responses are next in order: first an acceleration of pulse rate and decrease in pulse pressure, then a constriction of the finger and dilation of the chin blood vessels, followed by a slowing of pulse rate and an increase in pulse pressure. Finally in the series comes a shift to slower,

deeper breathing. The defensive response also includes a reduction in salivary and gastric secretions and slowing of digestive processes (*4*).

The defensive response largely involves the sympathetic nervous system but has some parasympathetic aspects. This response is not limited to a single organ system or structural division of the nervous system. It occurs independent of emotional response on the part of the subject. It is altered by sound intensity and band width in a dose-dependent fashion. It does not completely habituate (*13*), although under laboratory experimental conditions, substantial apparent physiological habituation has been reported (*14*). It also may be elicited by low levels of sound with special significance (*15*).

Under actual working conditions, the physiological effects of the defensive response were found in sawyers exposed to bandsaw noise (*16*). Another laboratory study noted a decrease in blood eosinophile level reflecting a stress response after 25 min exposure to 85 dB level noise (*17*).

The defensive response can become the stress that leads to the General Adaptation Syndrome that will be described more fully later with its alarm, resistance, and exhaustion stages if the sound stressor is of sufficient duration, quantity, and quality (*18*). When this takes place the hypothalamic-pituitary-adrenal axis is mobilized with resulting increase in adrenal cortisol and epinephrine output. During prolonged exposure to intense sounds, these endocrine effects may produce gastroduodenal ulcers and renal changes in laboratory animals (*1*).

Next we will enumerate the critical variables that determine whether or not sound stimuli become stressors that produce human stress.

Sound as a Stressor

Modern urbanization, crowding, the mass media, information technology, conditions of work and noise are overloading the human sensory environment (*19*). Of these stimuli our interest is in sound, particularly noise, although sound with meaning, such as speech, also can contribute to overloading an individual's processing capabilities. The progressive increase in noise from industrial, traffic and home sources, both machine and human generated, has reached offensive proportions in the United States (*20, 21*).

Noise essentially is unwanted sound. As such, subjectively experienced noise is any sound that produces annoyance or communication or task performance interference. The same sound stimulus may be perceived subjectively as noise by some and not by others. For this reason it is useful to define objectively experienced noise as sound that produces harmful bodily effects, which may or may not be subjectively perceived. This point is important because noise can be subjectively or objectively stressful, or both.

In information processing terms, noise is sound that overloads the central nervous system's pro- this state can be detected by changes in the electroencephalogram (*27*). The reception of a stimulus is influenced by two kinds of cognitive state characteristics, current transient influences and enduring qualities of the individual.

The first characteristics are transient influences that are more evident and easily measured than the second type. They include level of mental arousal, from sleep through alertness to anxiety; the context of sensory stimuli arriving through the other special senses; the motor context which includes ongoing task performance, the activities of the individual; the meaning of the stimulus evoked by associations from cerebral cortical memory areas; the degree of perceived control of the stimulus, whether one is able to control the situation is helpless or expects failures (*25*) and social values and attitudes toward the stimulus sources.

The level of mental arousal is influenced whether or not a sound stimulus is consciously perceived as a stressor. During the stage of early sleep, for example, sound can produce orienting and defensive responses and alter the quality of sleep without causing awakening. At the other extreme, an anxious individual can experience heightened sensitivity to a sound stimulus. For example, a study of college age males rated on an anxiety scale disclosed that for subjects rated high on anxiety, household noise levels were stressors as manifested by impaired task performance and subjective frustration (*28*).

The interaction of sound stimuli with other sensory stimuli may be significant. For example, related visual stimuli enhance the effect of sound. Clinically, sound can have an analgesic effect when certain intensities and frequencies occur in the presence of pain as is known in the practice of dentistry.

The ongoing motor activity of an individual influences cognitive state with higher levels of arousal by sound stimuli occurring while complex tasks are being performed and lower levels of arousal occurring when routine, monotonous activities are taking place.

For obvious reasons related to survival at a primitive level the meaning of sound is one of the most important factors that determines an organism's response. Threatening sounds of any kind portend potential danger, however, certain sounds acquire particular significance because of their symbolic meaning to the individual. Conversely, familiar,

repetitive sounds of moderate intensity cease to attract attention. Meaning connoting potential danger, then is related to unfamiliarity, rapid changes in intensity, or learned associations. For example, a study of evoked auditory potentials in the brain demonstrated that quickly changing acoustical events produce prominent cerebral excitation. The study also showed that sounds with symbolic meaning were perceived as more annoying than meaningless sounds of the same intensity and also produced larger evoked cerebral potentials (*29*).

Of particular importance is the fact that habituation does not occur to repeated novel laboratory stimuli that imply conflict or are coupled with an instruction to pay attention to that stimulus. Even covert associations with sound stimuli, such as a subject's attitude toward the experimenter, may decrease habituation (*8*). In addition, the symbolic meaning of a sound stimulus can evoke irrational responses, adding unconscious determinants of meaning (*30, 31*).

In addition to the meaning of the sound stimulus, a sound's predictability is an important determinant of response. In one study, unpredictable noise resulted in lower tolerance for frustration and greater impairment of performance efficiency than predictable noise (*32*). Furthermore, those investigators found that an individual's ability to control the noise source, and even the belief that one could, reduced the adverse impact of unpredictable noise (*8*). They postulated that the deleterious effects of noise were a function of unpredictability and the belief that one cessing capacity because it is too great in quantity, appears too rapidly or is dissonant in meaning or pattern. Noise is a commonly used standardized stressor in laboratory testing designed to evaluate human responses to stress (*5, 22*). In laboratory animals, for example, it is used as a stressor to produce lesions in the renal, reproductive and cardiovascular systems (*23*).

Another illustration of the use of sound is in stress studies such as the one by Cantrell, who exposed healthy young male volunteers to intermittent noise for several weeks (*24*). He found significant increases in plasma cortisol and blood cholesterol levels in addition to associated annoyance and sleep disturbance effects during prolonged exposure to bursts of 85 to 90 decibel noise.

We can use current approaches in stress research to facilitate our understanding of sound as a stressor (*22, 25*). In stress research the environmental conditions and the intervening bodily structures and processes that determine when and in what forms stress reactions occur are taken into account (*26*).

The work of Rahe, although encompassing life change in addition to sensory stressors, is particularly useful in identifying specific variables that should be taken into account in research on the human effects of noise. Rahe developed a life stress and illness model which identifies the key steps along a pathway extending from a person's exposure to a stressor to the eventual reporting of an illness (*25*). Rahe's model (Fig. 2) utilizes the analogy of a series of optical lenses and filters in which stressors are depicted by a series of "light rays" of different stimulus characteristics.

The influence of a person's perceptual state in altering the experience of a stressor is represented by a "polarizing filter" shown in step 1. Possible sensitization, or desensitization, of a person to a stressor is indicated by changes in the "light rays" as they pass through the filter. The psychological defense mechanisms which appear to be capable of "diffracting away" a stressor's impact are depicted

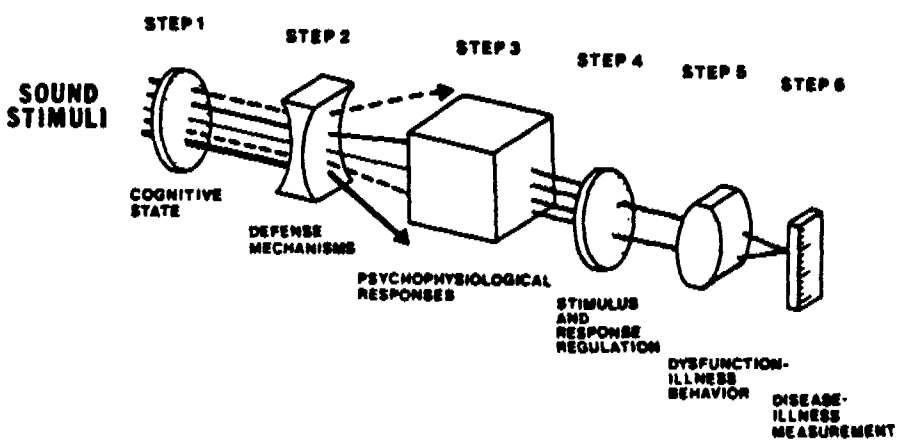

FIGURE 2. Rahe model of life stress and illness (*25*).

by the negative lens in step 2. Stimuli not so diffracted pass on to produce a variety of physiological reactions represented by the "black box" in Step 3. The wavy lines emerging from the black box cease to represent specific stressors and begin to indicate various psychophysiological responses to perceived and "undefended" stressors. Next a "color filter" shown in step 4 depicts how a person may cope with or absorb certain of these physiological reactions. Prolonged psychophysiological activations, if unabsorbed, lead to organ dysfunction and eventually to psychological and bodily symptoms. Symptomatic individuals may then seek medical care. A person's "focusing" of attention on symptoms is indicated by the illness behavior "positive lens" in step 5. If these symptoms are reported to health personnel, the person receives a medical diagnosis which then can be used as a measure of illness as represented in Step 6.

The value of Rahe's model is that it incorporates pertinent system levels in conceptualizing human responses to stressors, ranging from organ system to societal levels. It permits inclusion of both subjective and objective data as well. Furthermore, the model reflects clinical realities by recognizing the social factors that influence whether or not experienced dysfunctions become labeled as manifestations of illness. For these reasons, we will use Rahe's model to elucidate key variables in the human experience of sound as a stressor.

Cognitive State

Bearing in mind the preceding discussion of the characteristics of sound experienced as noise, the first step in processing a sound stimulus is the cognitive state of the individual. Some variations in this state can be detected by changes in the electroencephalogram (*27*). The reception of a stimulus is influenced by two kinds of cognitive state characteristics, current transient influences and enduring qualities of the individual.

The first characteristics are transient influences that are more evident and easily measured than the second type. They include level of mental arousal, from sleep through alertness to anxiety; the context of sensory stimuli arriving through the other special senses; the motor context which includes ongoing task performance, the activities of the individual; the meaning of the stimulus evoked by associations from cerebral cortical memory areas; the degree of perceived control of the stimulus, whether one is able to control the situation is helpless or expects failures (*25*) and social values and attitudes toward the stimulus sources.

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The importance of attitude toward the noise source is illustrated by another study in which a positive or negative attitude toward all aspects of one's community consistently influenced the reporting of perceived annoyance by noise positively or negatively (*35*). In the same vein, a Swedish study disclosed that propaganda promoting the importance of the air force diminished the reported annoyance levels in a community exposed to military aircraft noise (*36*).

The second kind of variables that influence the cognitive state of an individual are enduring background characteristics in the form of individual differences in temperament and cognitive styles, organic disease processes and mental illness.

Individual variations have been demonstrated in the ways that sensory stimuli are processed. Some individuals reduce and some augment the intensity of stimuli, leading to low or high sensitivity to a particular stimulus (*19*). Sensitivity to noise also is correlated with empathic, creative, intellectually oriented personality traits, confirming Schopenhauer's comment that "noise is a torture to people of great intellect" (*37*). Extraverted children may have a higher level of noise tolerance than introverted children (*38*). Moreover, individuals who express criticism tend to report annoyance by noise (*35*). Further evidence of individual differences in sensitivity to noise is reflected by the finding that some people thrive on noise which tends to synchronize their electroencephalograms while most people show electroencephalographic desynchronization (*39, 40*). At the other extreme, it is likely that 4 to 6 % of the normal population is "noise sensitive," in the sense that they do not adapt to noise at all (*8*). For all of these types of individuals, noise has implications detrimental to their mental health.

As an illustration of other background illness characteristics, one study showed that cardiac infarction and schizophrenic patients showed greater stress responses to noise as measured by cortisol and urinary catecholamine levels than did normal subjects (*41*). Similarly, persons with cerebral vascular disease were found to be more susceptible to the detrimental effects of noise than normal subjects (*42*). Another unique group of patients harmed by sound are those susceptible to audiogenic seizures. Some are affected by sounds that produce the startle response and others by sounds such as music (*43*).

The role of psychiatric status in sensitivity to sound was suggested in a study in which normal subjects and patients with specific phobias showed habituation of physiological responses to noise while hysterical patients did not. Moreover, patients with diffuse phobias, anxiety neuroses and agitated depressions all habituated more slowly than normals (*44*). In a general sense, another survey found that psychiatric patients were more annoyed by noise than normal subjects (*45*).

Defense Mechanisms

The next cluster of variables that influence an individual's response to sound stressors are internal defense mechanisms noted in step 2 of Rahe's model. In contrast with coping techniques which are directed toward changing the stimulus environment, the defense mechanisms are devoted to maintaining homeostasis or internal equilibria, within the person.

The defense mechanisms operate automatically and unconsciously. The most primitive is the acoustic reflect which offers a small degree of protection from high intensity sounds. Another example of a physiological defense is cerebral cortical inhibition such as was demonstrated in a study of laboratory animals exposed to extreme sound which ultimately produced convulsive seizures and lethal cerebral hemorrhages. This study found that a seizure producing epileptogenic focus of excitation arising in the medulla was actively inhibited by the cerebral cortex. When this inhibitory process was exhausted, seizures occurred (*46*).

In addition to these physiological defenses, psychological defenses shield the individual from physiological arousal and also play a significant role in reducing sensitivity to sound. For example, the psychological defenses of repression and denial can minimize physiological responses as was found in a study of patients in a coronary intensive care unit (*25*).

Psychophysiological Responses

The next level, step 3 in the model, comprises psychophysiological responses to sound stressors. The psychophysiological responses can be divided into two categories. First are responses within the awareness of the individual, such as sweating, change in heart rate and muscle tension. Second are those responses which occur outside of one's direct awareness, such as changes in serum lipids, cortisol, blood pressure and blood sugar levels.

The psychophysiological responses are manifestations of the defensive response to sound, can be immediate or delayed, and occur in interactional patterns. Thus, studies of single physiological responses oversimplify the mixture of responses. An example of an immediate psychophysiological response to noise is the finding of elevated diastolic and systolic blood pressures and urinary excretion of norepinephrine metabolites in brewery workers on days in which they deliberately did not wear hearing protective devices (*48*).

Genetic and constitutional individual differences may increase the likelihood that a particular organ system will respond to stressors more than others and over time lead to disease. There also may be a critical period during infancy in which visceral learning takes place, adding conditioning of an individual's disposition to the physiological responsiveness through a specific "target" organ system (*49*). For example, in certain predisposed individuals, the target organ is the cardiovascular system, and sound stimuli produce intermittent increases in blood pressure which may eventually cause structural changes in blood vessels leading to permanent hypertension (*50*).

Stimulus and Response Regulation

The next cluster of variables are stimulus and response reduction mechanisms. These coping techniques may deal with the stressor itself or with the physiological and emotional responses to it (*51*, *52*). Using ear protective devices is an example of dealing with the stressor itself by reducing the reception of the sound stimulus.

If one becomes aware of the psychophysiological responses, particularly if they are seen as threats to health, deliberate response management techniques can be employed. For example, muscle relaxation may "absorb" the muscle tension that contributes to elevation in blood pressure.

In a broader social sense, stimulus regulation can be achieved through an individual's participation in community, industrial and consumer efforts to acoustically condition home and working environments and manufactured products.

Dysfunction: Illness Behavior

In step 5 in the model, the lack or failure of defense mechanisms and regulation techniques play important roles in producing dysfunction. The concept of sensory and information input overload is useful in understanding how the central nervous system responds when defense mechanisms and regulation techniques fail to adequately screen incoming stimuli. In this conception sensory inputs are the sound stimuli and information inputs are sounds with symbolic, message containing meaning. Overload results from an excess of the number or rate of sensory or symbolic stimuli or both.

Human experiments have shown the disorganizing and psychotogenic effects of sensory overload. Experimental exposure to intense visual and auditory sensory overload produces dramatic effects in the form of heightened and sustained arousal, mood changes, illusions, hallucinations, and body image distortions (*19*).

Sensory and informational sound overload also are commonplace in modern, urban living (*53*). Jets, air compressors, sirens, rock and roll music and road traffic are generally unpredictable and often uncontrollable sources of stimulation that contribute to making the sound of our environment inimical to mental well being. Low frequency noises have effects similar to the more familiar piercing high frequency sounds (*54*, *55*).

A typical household vignette illustrates the unrecognized importance of sound sensory and informational overload in our lives. The washing machine provides a steady hum, the clothes dryer suddenly begins to vibrate; then the telephone jangles while the delivery boy rings the doorbell; a jet aircraft rumbles overhead and automobile horns are heard, a television set blares in the background; and amidst this confusion, children begin to fight, cry and scream. The overall noise level is not high by hearing damage risk criteria, but a homemaker can attest to the resulting frustration, irritability and even anger. Over time, one manages to adapt to this noise routine. However, one makes errors in balancing the checkbooks, screams at the children for minor transgressions, is irritable with one's spouse, and generally shows symptoms of stress by the end of the day. Furthermore, when one becomes resigned to a lack of control over one's environment, the resulting "learned helplessness" itself may become a stressor and contribute to additional symptoms of depression (*10*, *56*).

Selye's classic work on stress provides a framework for understanding the body's responses to sensory and information input overload (*18*). His terms stressor and stress are comparable to stress and strain in physics. In his view stressors produce two types of changes in the body. The first is a primary nonspecific change in an organ system called the "Local Adaptation Syndrome." This local adaptation occurs repeatedly in normal living. For example, running produces stress in the musculoskeletal and cardiovascular systems. The resulting exhaustion is reversible through rest.

The second change is the "General Adaptation Syndrome" which is activated by intense and persistent stressors that produce a specific effect on the adrenal glands, thymus and stomach. The fully developed general adaptation syndrome consists of three stages: an alarm reaction, a stage of resistance and an ultimate stage of exhaustion. Extremely severe stress can lead rapidly to exhaustion and death.

Stressors, then, set in motion adaptive responses which maintain biological and psychological homeostasis. In addition to specific organ system responses, a relatively stereotyped set of neuroendocrine reactions contribute to the development of the general adaptation syndrome. Most prominent are increased secretion of the adrenal cortical hormone, cortisol, and increased activity of the sympathetic nervous system, including increased secretion of epinephrine by the adrenal medulla. The increase in sympathetic nervous system activity prepares the individual for "fight or flight." The net effect of these responses is to mobilize nutrients, such as glucose from the liver and fatty acids from fat tissue, to "arouse" the central nervous system, to provide more oxygen and nutrients to skeletal muscles, to increase contractibility of skeletal muscles and to increase coagulability of the blood. When these responses are persistent, the sustained effects of cortisol may appear in the form of gastric ulceration, inhibition of immune responses, hypertension, atherosclerosis, sterility and personality changes (*57*). Most stressors act for a limited time and produce changes corresponding to the first and second stages of Selye's syndrome. The complete general adaptation syndrome results in a specific set of physical changes: enlargement of the adrenals, shrinkage of the thymus and lymph nodes and ulceration of the stomach.

Selye's conception helps to explain that subjective experience and physiological responses to stressors can appear to have returned to normal or pre-stressor levels during the second stage of resistance. This point is essential in understanding the phenomenon of habituation which has been repeatedly observed in experimental studies of human responses to sound as a stressor (*8, 14*). Habituation may reflect the completion of a local adaptation syndrome cycle with restoration of normal bodily functioning. On the other hand, it may reflect a stage of resistance during which the body is moving into the full general adaptation syndrome which gains a momentum of its own and exacts a physiological cost through the development of dysfunction of the various organ systems.

A stimulus appraised as threatening gradually loses its capacity to arouse an emotional response if it is reappraised on repetition as less harmful and results in adaptation (*26*). This surface adaptation may be deceptive, however, and continued exposure to the stressor may produce cumulative effects that appear after stimulation is terminated. This may be in the form of strain induced by the adaptive responses themselves. In spite of adaptation, then, stressors may cause biological and behavioral aftereffects following cessation of the stimulus (*8*).

Laboratory studies of the physiological and behavioral reactions to noise indicate that adaptation (habituation) generally takes place in healthy subjects. There is laboratory evidence, however, which suggests that some components of physiological responses to noise do not habituate completely (*58*), although this work has been questioned (*14*). It is important to distinguish between the tension response of an organism to stressors and stress which is a dangerous condition resulting from failure to manage tension effectively (*59*).

Another factor should be taken into account. More than lower animals, human reactions to stressors not only depend upon the direct impact of stimuli themselves but also on associated cues that signify the meaning and consequences of the stimuli. Human stress, therefore, must be defined in terms of transactions between a stimulus and an individual's reaction to the situation.

The fact that sound stimuli are processed cognitively, therefore, introduces the important conception that psychological stressors, such as the anticipation of harm, can strongly influence human responses to sound stressors (*52*). Activation of the neuroendocrine system usually depends upon the individual's recognition of a stressor as a threat. The auditory system, however, like heat or cold stressors, automatically activate the reticular activating system and thence can evoke autonomic-neuroendocrine responses.

Dysfunction resulting from sound stressors, then, may be the direct result of the sound stressor situation or may indirectly result from the activation and progress of the general adaptation syndrome. Dysfunction may be subjectively experienced

as symptoms, for example, annoyance and tinnitus, or be objectively demonstrable as physical signs, for example, elevated blood pressure and hearing loss. At the same time subjective reports of interference with task performance and speech communication also can be accompanied by objective changes in cerebral responses on the electroencephalogram (*27*).

Human dysfunction can be categorized according to the influence of noise on five basic, interrelated functions that influence the well being, or mental health, of an individual: (1) hearing, (2) sleep, (3) task performance, (4) speech communication and (5) emotional state.

Hearing. The effects of noise on hearing in the form of temporary and permanent threshold shifts and progressive deafness are well documented (*60-62*). There are three levels of hearing at which loss of acuity can occur: the primitive, warning, and symbolic (*63*).

The primitive level includes the familiar background sounds of one's every day environment. Loss at this level constitutes a form of sensory deprivation and may lead to a sense of isolation. Loss of hearing at the warning level contributes to a sense of insecurity and physical vulnerability in the environment. Loss at the symbolic level interferes with interpersonal communication and may result in social isolation, withdrawal and depression. Overlap between levels of hearing loss magnifies the psychological impact on the affected individual.

In addition the need to wear a hearing aid in itself may cause self-consciousness and undermine self-esteem. The emotional and psychological reactions to hearing loss accordingly are threats to an individual's mental health (*13, 64, 65*).

In a more general vein, the loss of hearing with aging (prebycusis) has been related in part to noise exposure in urbanized societies (*66, 67*).

Sleep. Chronic sleep disorders detrimentally affect health and well-being. A major portion of complaints about noise arise from disturbance of rest and sleep (*31*). The Environmental Protection Agency Urban Noise survey found that 28% of the sampled population experienced sleep disturbance which also was rated as the most annoying effect of noise (*20*). Similar findings have been reported by other surveys (*68-71*).

The electrophysiological response to noise tends to decrease during exposure to noise during sleep, however, autonomic responses do not (*31, 72*). This has been shown in a study in which cardiovascular responses did not habituate to traffic noise experienced by sleeping subjects (*73*). In sleep, noise evokes the same orienting response in the form of EEG arousal and changes in heart rate, GSR and finger vasoconstriction as during waking without its voluntary motor component (*31*).

The evidence also is clear that noise exposure during sleep lightens the level of sleep, especially for subjects of an anxiety-introversion personality type (*27, 70, 74*). Sleep disturbances have been reported in response to low frequency noise in the 20-1000 Hz range (*55*). Intermittant noise above the mean background level has a greater effect than louder, more continuous noise on vegetative functions (*75*). Age and sex in addition to sleep stage are critical factors in determining the physiological responses of noise sensitive individuals. Older subjects and women are more sensitive than younger subjects and men. Moreover, sounds with meaning tend to awaken subjects at lower intensities than those without meaning (*76*).

A study devoted to the next day effects of noise-exposed interrupted sleep showed impaired performance of tasks affected by the lack of sleep. There also is suggestive evidence that noise experienced during the waking hours may reduce the duration of sleep of susceptible persons (*77*).

All of these findings suggest that susceptible persons may be affected by noise occurring during sleep as well as during the waking state. For night workers, mothers with babies and elderly persons, day and nighttime noise can be a significant problem (*31*).

Task Performance. There is little evidence that significant performance impairment on simple tasks occurs under continuous noise below 80 to 90 dB (*77*). Unpredictable or intermittent noise, however, does affect performance at even lower levels (*78*). It is well established that noise has a negative effect on work tasks that involve listening or conversing (*79*). Adverse effects occur with complex, multicomponent tasks that require prolonged vigilence or continuous performance and those in which information content is high. Under these circumstances, impairment of task performance persisting after exposure to noisy environments has been reported (*80, 81*).

Evidence has accumulated regarding noise interference in the school performance of children When children are involved in complex activities requiring precise movements and intense concentration, noise produces inattention and impaired task performance (*82, 83*).

A study of the effects of noise generated by expressway traffic in homes showed higher reading achievement for children exposed to lower ambient noise levels (*84*). Another study suggests poorer task performance by young children from noisy than quiet homes (*85*).

A study compared children from schools and

homes with noise levels of 87-99 dBA with those of 48-65 dBA levels. The children in the noisy environments showed increased distractibility and impaired achievement in school. Over a period of four years they became more distractible, indicating increased sensitivity to noise with the passage of time (*86, 87*). Children exposed to high noise levels in schools also attain lower reading achievement than those with low noise levels (*88-90*).

One study of preschool children found that reflex motor reactions to sound and light stimuli were delayed in those exposed to moderate background levels. The children with the higher noise level required more time in task performance as well (*91*).

All of these performance effects influence an individual's attitude toward work and may constitute additional stressors in themselves, contributing to frustration and stress reactions.

Speech Communication. Interference with communication through speech not only creates personal frustration but has consequences in social interaction. Individuals react to noise levels that do not completely interfere with intelligibility. Noise accordingly may reduce efforts to converse, lead to repeated speech, and ultimately to withdrawal (*92*). The hearing impaired are particularly susceptible to these reactions (*93*). Interference with communication between teachers and children in air traffic exposed schools also has been found (*94*).

Children's speech acquisition and language development may be impaired since the repetition of speech needed to develop these skills is reduced as background noise level increases. Noise accordingly may interfere with the perception of speech by young children and affect the acquisition of language. More than adults, children depend upon the clear perception and repetition of speech sounds during early learning periods (*61*).

Emotional State. The most prominent subjective emotional response to noise is annoyance, a commonly reported but difficult to describe and quantify emotional state. Research on annoyance is hampered by the ambiguity of the term and the fact that one can be annoyed by noise itself or by its symptomatic and behavioral consequences. Arhlin relates annoyance to the direct effects, such as hearing loss, sleep, task performance and speech interference, and the indirect effects of noise, such as blood pressure elevation, headaches, fatigability, anxiety, depression and accident risk (*95*).

A standardized definition of annoyance is needed because each study tends to report annoyance in a different way. In its most specific sense annoyance is an emotion with a protective function. It motivates an individual to try to avoid or influence the sound stressor. Like discomforts such as pain, chill and warmth, annoyance serves to warn an individual of unpleasant or harmful environmental conditions. Annoyance also can be produced by interference with task performance sleep and somatic symptoms. The direct experience of annoyance by noise itself differs from indirect annoyance because of a headache.

Annoyance directly related to noise, then, is an unpleasant emotion experienced as irritability and is a form of anger or hostility related to the state of the individual in a particular social and environmental context. For example, the sound of the barking of one's own dog may be less annoying than the barking of a neighbor's dog. In another vein, some experimental subjects refused to continue in a noise study because they perceived it as unpleasant (*8*). There also is a tendency to regard sound as noise at work more than at home (*96*). Because of this relationship to the peculiarities of the context, annoyance can be expected to vary in its occurrence and reporting.

Annoyance is heightened when noise is perceived as unnecessary; when those responsible for the noise are perceived as unconcerned about the exposed population's welfare; when other aspects of the environment are disliked; when noise is believed to be harmful to health, and when noise is associated with fear (*10*).

Although defined differently from study to study, annoyance is a commonly used concept in surveys of community responses to noise. The tendency is to define annoyance of the respondents in terms of physiological responses, although a scale has been developed that excludes somatic symptoms (*45*). It can be inferred then that the more annoyed a respondent the greater the physiological reactions the person is experiencing. Direct physiological measurements would be preferable to subjective reports, however, the stage of this research is not sufficiently advanced to permit the specific measurement of noise induced stress isolated from other environmental stressors.

The evaluation of annoyance is further complicated. Not only is it an ambiguous concept, but respondents are influenced by the questions they are asked. For example, more positive responses were obtained when people were asked if aircraft noise produced specific symptoms than if asked about symptoms without suggesting a connection to aircraft noise (*97, 98*). When annoyance was analyzed according to attitude, activity interference and symptoms, McKennel found that 65% of his sample reported feeling annoyed, 35% reported interference with activities and 5% reported symptoms (*99*).

Although methodological problems are important in assessing studies of reported annoyance due to noise, a number of surveys suggest that between 30% and 40% of urban dwellers are regularly annoyed by noise (*20, 21, 31, 96, 100*). In the flight pattern of Heathrow airport in London, 65% reported annoyance (*99*).

Noise in industrial situations also may induce what has been described as an "astheno-vegetative syndrome" in the form of increased fatigability, decreased capacity for focusing attention and slowing of motor reactions (*101*).

Disease: Illness Measurement

In step 6 of the model, whether or not people define themselves as ill depends upon individual and cultural attitudes toward assuming the patient role. These personal and social factors influence whether or not an individual minimizes or exaggerates symptoms and adopts "sick" behaviors such as missing work and seeking health care. The critical step for defining illness, then, occurs when health care is sought and a diagnosis is established. This point is the entree for measuring illness resulting from sound induced stress.

There is an inevitable gap between laboratory studies of the immediate and delayed effects of noise on health. Still, some investigators regard noise pollution in densely populated areas as a social danger comparable to that of known ingested carcinogens and air pollutants (*102*). Imposing problems, however, stand in the way of proving this thesis as illustrated by methodological criticisms of a study which found that people residing near the Los Angeles International Airport had a higher death rate from stress related diseases than a control population (*103*).

More specifically, European research on industrial noise has identified a cluster of symptoms encountered by physicians and referred to as "noise sickness" (*31, 104*). This syndrome is manifested by tinnitus, increased sensitivity to noise, fatigability, lowering of general resistance to illness, headaches, irritability, sleep interference, "heart pains," weight loss, tremors, digestive disorders and ultimately hearing loss. These symptoms are based upon the stress responses of the auditory, autonomic, cardiovascular, endocrine, and gastrointestinal systems and precede the actual loss of hearing.

Although short-term studies show that work performance can be maintained under noisy conditions, the more important consideration is the long-range effect of noise on health. The European data appear to show that complete physiological and psychological adaptation to prolonged noise exposure does not occur. The person reacts unfavorably to noise from the beginning, and adverse reactions progressively increase with the passage of time. This is most evident in work requiring complex task performance. Because of the cumulative negative effect on one's state of health, the adaptation of many individuals working in noisy environments exacts a health cost (*101*).

For convenience we will briefly summarize the relationship between noise exposure and (1) mental illness, (2) cardiovascular disorders, (3) gastrointestinal disorders, (4) neurological disorders and (5) fetal abnormalities.

Noise and Mental Illness. The role of noise in mental illness is most difficult to assess. Several studies of mental hospitals in the vicinity of Heathrow Airport in London disclosed a small but significantly higher admission rate than those in less noisy areas (*105-107*).

Another piece of evidence relating a form of mental illness to noise is through an indirect relationship between noise induced hearing loss and mental illness. Acquired deafness forces a change in life style toward greater social isolation and leads to an over-representation of mental illness in deaf people of all ages. One study found that 46% of a group of elderly deaf persons were paranoid and 21% had affective disorders (*65*).

On the other hand, noise-related annoyance in itself probably is not a cause of mental illness, although psychiatric patients do constitute a vulnerable group to the adverse effects of noise. Somatic and emotional symptoms associated with annoyance by noise are significant, however (*45*). The consumption of tranquilizers and sedatives has been used as an index of these symptoms resulting from noise exposure. Greater usage of these medications have been found in air and road traffic areas exposed to high levels of noise (*69, 99, 108, 109*).

Noise and Cardiovascular Disorders. There is a consistent correlation between prolonged exposure to high intensity industrial noise and an increased prevalance of hypertension, as demonstrated by over 40 studies (*110*). The risk increases with advancing age and increasing years of employment for both men and women. The risk also is greater under circumstances of intermittent impulse or impact sound than continuous or relatively steady sound. There is significant confirmation under actual living and laboratory conditions of the association between high intensity sound and cardiovascular disorders in children and adults (*10, 69, 111, 112*.

More specifically, prolonged noise exposure produced sustained elevations in blood pressure in a controlled experimental study of Rhesus monkeys. A carefully designed and monitored study of mon-

keys exposed for nine months to a continuous noise environment simulating that of urban factory workers disclosed significant, sustained elevations in blood pressure levels and alterations in diurnal blood pressure rhythms (*113*). These changes persisted after discontinuing exposure to the noise environment, suggesting a basis for long-term noise effects on the cardiovascular system in humans. Since Borg's study disclosed that lifelong exposure to high noise levels did not produce hypertension in rats (*114*), this study of primates is important because it bears a closer relationship to the human situation.

The fact that all persons exposed to noise do not show cardiovascular disorders is consistent with the likelihood that noise affects the health of susceptible individuals when combined with other stressors, such as work pressure and population density. Furthermore, environmental stressors are most likely to affect people who are unable to control them. Thus, people in institutions, with low incomes and low levels of education and children are especially likely to show adverse reactions from noise exposure (*10*).

Noise and Gastrointestinal Disorders. The data presently available are insufficient to justify judgments about the role of long term noise exposure in gastrointestinal disorders (*110*). The European literature on industrial noise, however, strongly suggests such a relationship (*10, 101*).

Noise and Neurological Disorders. A number of investigators report neurological changes associated with long-term occupational noise exposure (*110*). The principal signs include: autonomic imbalance such as dematographism, hyperreflexia, hyperhydrosis, and hand and eyelid tremors; an altered sense of balance; decreased tactile sensitivity of the hands and feet; decreased stimulus reaction time; a decreased reactivity to visual stimuli; and obscuring of regional activity in the electroencephalogram.

An uncommon neurological disorder that is directly affected by auditory stimulation is the audiogenic seizure syndrome (*43*). In individuals with this disorder seizures are precipitated by certain sounds.

Noise and Fetal Abnormalities. The human fetus perceives and responds to environmental sound in utero as reflected in motor activity and heart rate change. In the last trimester of pregnancy, the fetus can be conditioned by external sound stimuli. Maternal anxiety related to noise can produce increased fetal activity. A possible subtle prenatal effect of maternal anxiety induced by noise exposure could be infants who are hyperactive and have dysrhythmic temperaments (*115*).

In experimental animals, maternal and fetal abnormalities have been linked to noise (*116*). At this time, however, the evidence of the adverse effect of noise on the human fetus is suggestive but not established (*117, 118*).

In summary, the data on the health effects of noise indicate that sound exposure of more than 3 to 5 years with intensity levels of 85 dBA to 90 dBA is associated with increased health risk. Furthermore, the adverse physiological effects of noise surface before damage to hearing appears suggesting that attention to the physiological effects of noise may well enhance the prevention of noise induced hearing loss.

The effects of noise on children deserve special attention because children do not spontaneously report them, have little awareness of their significance and cannot significantly influence their environments. The evidence is that children may be particularly susceptible to noise-induced developmental and learning impairment which have long-range implications for later life (*10*).

For those who choose to question the health implications of noise, we must recognize that positive proof of cause and effect between a stimulus and human disease can never be established in the strictest experimental sense because of the multitude of intervening variables. Research in the health sciences differs fundamentally from that of the physical sciences. In even the most sophisticated epidemiological survey, a correlation remains a correlation. Species differences always exist and must be considered in even the most convincing animal study. For ethical reasons these are the only kinds of research evidence we are likely to have. We need further research to illuminate specifics but not to prove that noise is a significant threat to human health.

Implications

Our thesis is that research on, and efforts to prevent or minimize, the harmful effects of noise have suffered from the lack of a full appreciation of the ways in which humans process and react to sound. In an effort to stimulate more comprehensive approaches, we have described an integrated model of the auditory processing of sound based upon current knowledge of neuroanatomy, neurophysiology, neuroendocrinology and human stress.

Piecemeal research on narrow aspects of noise-related problems has led to conflicting conclusions that either minimize or exaggerate the significance of noise for physical and mental health. The designation of the general physiological effects of sound as "nonauditory" has been particularly misleading

to the general public. Because of this fragmentation and ambiguity, definitive action has been stymied by misunderstanding of the economic, social, and personal costs of noise control efforts. Underlying the confusion is the failure to appreciate that, beyond human communication, sound plays a vital role in the physiological functioning of the body.

As is true with other human problems, additional inevitable resistances to facing and remediating the untoward effects of noise have been encountered. This is particularly because the root causes of noise pollution are the imposition of modern technology and population pressures on natural human living conditions. Solutions accordingly require adjustments in styles of behavior and living. Even though short range inconveniences may lead to long range benefits, the human tendency is to resist change and maintain the status quo. Workers fail to wear protective hearing devices, manufacturers do not acoustically condition products and government does not adequately enforce standards. Moreover, the human capacity to adapt to noisy environments masks the magnitude of the problem. Hearing loss in itself further may reduce awareness of noxious sounds. These resistances are important determinants of ambiguities in the measurement of community responses to noise (*119*).

We believe that the paralysis of effective action is not a result of lack of knowledge but of a failure to integrate and articulate existing knowledge so that compelling reasons can stimulate the motivation needed to implement changes. For this reason, education of the public and workers in the field is the most important need today.

The compelling reasons for action are the facts that substantial groups of the population are vulnerable to adverse health effects from noise, that the quality of life is generally eroded by annoyance from noise, that sleep is disrupted, that productivity is reduced, and that the education of children is affected by noisy environments.

Without question noise can be a stressor and consequently an important underestimated pollutant of modern society as are chemicals and particulate matter that pollute the air, water, and food. Moreover, noise significantly affects the human nervous and endocrine systems. Because these systems are capable of sophisticated short range adaptive maneuvers, the harmful effects of noise, like other pollutants, usually become evident at later points in time. Noise is one of the main sources of sensory overload for city dwellers and industrial workers (*19*).

More than other pollutants noise interacts with other sensory stressors, population density, life change and life circumstances. Thus, noise plays an aggravating role in addition to stress generated by environmental conditions and attitudes toward them. These complex interactions have led to despair in ferreting out the exact role of noise in stress induced dysfunctions. When seen in the context of all of these factors, however, noise often emerges as the one most accessible to preventive and remedial action. This is reflected in the already existing federal, state, and local noise control measures. Actually, there is little more that needs to be known. The problem lies in the lack of coordination between acoustical engineering, urban planning, health, architecture, audiology, and other related professional disciplines.

There are essentially three points of intervention in noise control: reducing sound emission from the source, blocking sound transmission from the source to the ear, and protecting the ear itself from receiving the sound. Practical considerations limit the reduction of sound emission from industrial, traffic and aircraft sources. Still, acoustical conditioning of working and living environments can effectively reduce transmitted sound. Finally, sound can be effectively blocked at the level of the ear through protective hearing devices. By intervening at any or all of these levels there are few noise problems that cannot be effectively managed today. Thus, the problem is not that remedies are unavailable or too costly, but that the least expensive ones are not being used.

The multifaceted nature of solutions to the noise problem involves the cooperation of those who generate and those who are affected by noise. We cannot realistically expect dramatic reductions in the sources of noise pollution (*120*). Unlike other forms of environmental pollution, however, individuals can minimize the adverse effects of noise upon them. To the extent of economic feasibility industry should more actively reduce noise emission at the source by machines, vehicles, and appliances. Beyond that point, individuals can and should protect themselves from harmful sounds through acoustical conditioning and sound occluding ear devices.

The fundamental problem is one of attitude at the levels of government, industry, consumers, and health care workers. Noise already has been identified as a national hazard by Congress in the form of the Noise Control Act of 1972 and the Quiet Communities Act of 1978. Federal standards for new product noise emission, labeling requirements, and state and local regulations are being promulgated (*121-123*). Yet unachieved, however, is public awareness of the significance of noise pollution. An attitude of helplessness prevails leading to either resignation to the existence of noise or escape from it by

moving out the urban areas or changing jobs. Unappreciated is the fact that citizen initiatives, community organization, labor union bargaining, consumer demand, and personal efforts can create a climate in which an attitude of mastery over noise rather than helplessness can be achieved.

The basis now exists for public, consumer and labor expectations that acoustical conditioning be given priority equivalent to air conditioning in housing and industrial construction and in machine and appliance manufacturing. The problem lies simply in a lack of awareness of the importance of these factors. People have become accustomed to accommodating to noise through bodily defense mechanisms and lack an understanding of the personal and governmental resources available to them. Citizens do not fully appreciate that, negative research findings and preoccupation with the details of measuring community annoyance notwithstanding, they have the right to determine the quality of their lives and to be free from the harrassment of noise generated by industrial, vehicular, office, airport, and household appliance sources.

Summary

The fundamental purposes of hearing are to alert and to warn. The auditory orienting response, startle reflex and defensive response translate sound stimuli into action and sometimes into stress induced bodily changes. In the course of human evolution the additional purposes of communication and entertainment developed as sound assumed symbolic meaning.

The brain's processing of sound has been outlined as the biological and psychological basis for the effects of sound on the body. An integrated model then was presented for analyzing the impact of sound as a stressor on the body and for identifying key variables for research on the health effects of noise. In addition to the characteristics of the sound stimulus, a variety of personal and social factors determine whether or not noise becomes a stressor. The cognitive state, defense mechanisms, psychophysiological responses and stimulus and response regulation techniques of the individual person play vital roles. When the tension induced by sound persistently alters the homeostasis of the neuroendocrine system, a state of stress results with accompanying dysfunction in hearing, sleep, task performance, speech communication, and emotional state. When dysfunction leads to the assumption of the patient role, stress induced illness can be identified in the form of the suggested syndrome of "noise sickness;" cardiovascular, neurological, and gastrointestinal disorders; and possibly aggravated mental illness and fetal abnormalities.

Noise is a stressor and an important, largely unrecognized, pollutant of our environment. Our quality of life generally is eroded by annoyance from noise, and substantial segments of the population are vulnerable to its adverse health effects. More specifically, sleep is disrupted, productivity is reduced and the education and development of children is affected by noisy environments.

The prevention and reduction of noise pollution need not await further knowledge. The technology for reducing noise emission, acoustically conditioning environments and protecting hearing now exists. The problem is the lack of public awareness of the significance of noise pollution and solutions to it. The challenge is to convert through education a public attitude of helplessness to one of mastery through citizen initiatives, labor union bargaining, consumer demands and personal efforts to adopt the most feasible noise and noise response control measures.

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