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July 19, 1988

Robert A. Bunda, Esq.
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One SeaGate, 17th Floor
P.O. Box 2088
Toledo, OH 43603

In Re: Dendinger & Wallace, et al. v. Chrysler, et al

Dear Bob:

Pursuant to our telephone conversation yesterday, this letter is for the purpose of confirming your agreement to provide me with all of the articles and other information upon which Dr. Doll will base his expert opinions on the day prior to your taking of his deposition. Please be advised that I would like to review all of these materials at Dr. Doll's office beginning at 1:00 p.m., London time, on July 25, 1988. This assumes, of course, that the District Court will overrule my motion for a protective order and allows the videotaping to go forward on July 26.

Very truly yours,

MURRAY & MURRAY CO., L.P.A.

By
Kirk J. Delli Bovi

KJDB:sg

PLAINTIFF'S EXHIBIT Doll-1

URL 11692

CANCER DEATHS AMONG FORMER, WHITE MALE, CHRYSLER PLASTIC PRODUCT CORPORATION EMPLOYEES

	Respiratory Cancer		Other Cancer		Total Cancer	
	Observed Deaths	Expected Deaths	Observed Deaths	Expected Deaths	Observed Deaths	Expected Deaths
Coating/Finishing (Wallace)	4	1.40	3	2.47	7	3.87
Inspection/Shipng (Dendinger)	2	1.17	5	1.95	7	3.12
TOTAL	6	2.57	8	4.42	14	6.99

Medicina del Lavoro
March 1970
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pp 174-179

Istituto di Patologia General dell'Universita di Perugia
Direttore: Prof. A. Caputo

PATHOLOGY OF VINYL CHLORIDE

P. L. Viola

During the last years a syndrome characterized by alterations of the skeleton, teguments, nervous system and hepatic function[1, 2, 3, 4, 5, 6] has been observed among the workmen associated with vinyl chloride polymerisation process. An experimental programme has been performed in order to evaluate the toxic effect of vinyl chloride on the animal organism, and in order to try to reproduce in rats the acroosteolytic lesions observed in man.

MATERIALS AND METHODS

Twenty-five Wistar male albino rats, of average weight 150 gr., were exposed to vapours of vinyl chloride 4 hours a day for 5 days a week during 12 months. The animals were kept in a plastic air-tight container through which there was a constant flow of air containing 3% in weight, equal to 30,000 p.p.m. of vinyl chloride. At the end of treatment the surviving animals were killed at twenty-day intervals, and the paws, brain, liver, kidneys and thyroid were examined histologically after fixation, inclusion and colouration by the ematoxylin-eosine. Van Gieson, PAS, Weighert, Bielschowsky-Gemori methods. Twenty five rats of the same breed were set aside as a control.

RESULTS

During the period of exposure the animals were slightly soporific, but the first few months of treatment were well tolerated and the rats showed no change in body growth or behaviour and no organic alteration visible macroscopically or by radiological means. After ten months some of the animals began to show a decrease in weight, in agressiveness, in their reaction to external stimuli, and often a disturbed equilibrium. Thirteen animals died from cardio-respiratory complications. Two animals died from hemato-peritoneum. Most of the animals showed pathological involvement

of the brain, liver, kidneys, and thyroid. Six rats showed histopathological alterations of the skeleton.

The small metatarsal bones showed an extensive periosfal proliferation of cartilage-like material apparently originating by metaplasia directly from the bone. All around the newly formed cartilage the cellular components were compressed and arranged tangentially to the cartilage itself, forming a perichondral layer. The isogenous cartilagenous groups were irregularly arranged and their nuclei were of varying size and often number per cell. The edges of the cartilage were irregular, showing digital extroflexions resulting from a varying growth potential. There was also evidence of chondroid metaplasia in areas of mature compact bone, in which the cartilagineous elements were grouped around a central nucleus of bone, as in typical osteochondromatosic processes. In the small bones the chondroid metaplasia was often vary extensive and the bones seemed to be impregnated with a mucoid substance which altered the characteristic disposition of the bone tissue obliterating the cement lines. The skin of the paws showed areas of hyperkeratosis superficial thickening of the epidermis, vacuolization and degeneration of the basal layer, disappearance of the cutaneous adnexa and modest accentuation of the papillar layer of the derma. An almost constant state of edema was observed in the epidermic zone. The connective tissue showed dissociation of the collagen bundles and a diminution and fragmentation of the elastic reticulum. The small arterial vessels showed signs of endothelial fibrosis with a thickening and dissociation of the elastic membrane, often accompanied by a partial hyaline degeneration and homogenization of the walls and proliferation of the endothelium. Some of the vessels appeared completely blocked by a proliferation of the connective tissue in a formation not unlike that of onion skin.

The small nerve bundles were often surrounded and invaded by fibrotic processes. A microscopic examination of the brain revealed diffuse degenerative lesions of the grey and white matter. The external granular layer was often reduced and in some areas this was true also the medium sized and giant cells. Numerous examples were found of hypercoloured, atrophic neurons with disappearance of the nucleoli and sometimes also of the nucleus itself. At the level of the white matter there were zones of intense, reactive gliosis consisting for the most part of cytoplasmic and fibrillar astrocytes, some of which were arranged in a concentric disposition around the blood vessels. There was evidence of neuronal phagokaryosis with satellitosis and the deposition of neuroglial elements around the altered nerve cells.

There was modest proliferation of microglial elements, especially in areas of more intense gliosis and zones of intense spongiosis showing an accumulation of astrocyte-type elements with basophilic cytoplasm and abounding in gemistocytic and microglial elements similar in appearance to "scavenger" cells. The cerebellum showed signs of atrophy of the granular layer which was often represented only by a few isolated nuclei. The layer of Purkinje cells was in some places profoundly modified, the cells appearing to be undergoing intense degeneration and all the various stages of this process were observed, from the whole cell to the small homogeneous bodies with indistinct outlines which represent the most damaged form of the cell. Except for small and limited areas, the molecular layer seemed to be well preserved.

The liver was often of increased volume, sometimes subicteric in colour, with a smooth surface and somewhat more brittle consistency than normal. A histological examination showed in the majority of cases signs of diffused interstitial hepatitis with numerous hepatic cells in the grip of regressive processes varying from torbid degeneration of the cytoplasm to necrosis with marked cytoplasmic and nuclear polymorphism. Some of the hepatocytes showed giant or double nuclei. In these areas of cellular necrosis a corpuscolar exudation was always present consisting of round cellular elements of the lymphocyte or plasmacellular type. There was evidence of an abnormal proliferation of the Kupffer's cells, which were often hypertrophic. The triangular spaces appeared to be increased by the infiltration of round and polynucleated cells and eosinophiles showing marked polymorphism. The portal capillaries, centrolobular veins and sinusoids were often blocked by numerous centrally-located areas of partial necrosis, often accompanied by a diffuse steatosis in the form of small drops with clearly-defined areas of acidophile necrosis and the formation of elements similar to the round acidophile bodies of viral hepatitis and the "Cauncilman" bodies of yellow fever. In certain cases evidence was found of an intense fibrosclerotic reaction alongside the degenerative processes.

The kidneys did not appear to be excessively altered by the prolonged treatment with vinyl chloride, although they showed signs of tubulonephrosis, sometimes accompanied by chronic interstitial nephritis.

The thyroid often showed a colloid goitre and a marked increase in parafollicular cells.

The control animals showed no histopathological alterations of the skeleton or of the various organs.

CONCLUSIONS

This research confirms that the animals are sensitive to the toxic action of vinyl chloride. The lesions of the bone and connective tissue are similar to those noticed in experimental osteo-latyrism and to those described in a man affected with acroosteolysis of the hands (Marin). It should be pointed out that the roentgenological findings of skeleton in man rests on cartilaginous transformation of the bone tissue. Therefore according to reccomendation made at XVI International Congress on Occupational Health of Tokyo (1969) I should like some precautions to be taken in the manufacturing plants polymerizing vinyl chloride, such as reduction of the threshold limit value of monomer, and substitution of manual cleaning of autoclaves by automatic devices.

SUMMARY

The results of this investigation show that animals exposed to vapours of vinyl chloride may show degeneration of the skeleton and connective tissue with histopathological pictures similar to those observed in human acroosteolysis of the hands. The bones in fact undergo processes of intense periostium growth and diffuse, chondroid metaplasis. The connective tissue is dissociated into collagen bundles with a reduced number of cells, the plastic reticulum is markedly reduced and fragmentary, the small vessels of the deep layers of the derma show hypertrophy of the walls with a diminution and sometimes obliteration of the lumen, the nerve endings are surrounded and infiltrated by fibrous tissue. Degenerative processes of the parenchyma were observed in the brain, in the liver and in the kidneys.

NOTE: Figures on available copy were not suitable for reproduction. They are as follows:

Fig. 1 -- Periostal proliferation of metatarsal bone of a rat 16th months old, exposed to vinyl chloride vapours for 12 months

Fig. 2 -- Periostal proliferation of metatarsal bone of a rat, 16th months old, exposed to vinyl chloride vapours for for 12 months

Fig. 3 -- Periostal proliferation of metatarsal bone of a rat, 16th months old, exposed to vinyl chloride vapours for 12 months.

Fig. 4 -- Chondroid metaplasia in mature bone of metatarsus of a rat, 16th months old, exposed to vinyl chloride vapours for 12 months

Fig. 5 -- Chondroid metaplasia in mature bone of metatarsus of a rat, 16th months old, exposed to vinyl chloride vapours for 12 months

Fig. 6 -- Chondroid metaplasia in mature bone of metatarsus of a rat, 16th months old, exposed to vinyl chloride vapours for 12 months

Dell-6

Chimyalcik ALL-STATE LEGAL SUPPLY CO.

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Plaintiff's Ex. Fisher 7

MEMORANDUM

November 23, 1971

TO : Dr. G. H. Bernold, NYO-4
Mr. H. F. Eisenhour, 511
Mr. R. I. Hanna, 511
Dr. E. O. Hull, 514
Mr. G. R. Kraft, 514
Dr. K. S. Lane, NYO-4
Dr. W. R. Manning, 511
Dr. A. B. Steele, NYO-28

SUBJECT: Manufacturing Chemists Association Occupational Health Committee - Vinyl Chloride Conference

Companies with interest in vinyl chloride were invited to send representatives to consider the following:

1. Continuation of the Acroosteolysis Registry Program.

2. Review the reports of Dr. P. L. Viola on the development of tumors in rats exposed to vinyl chloride monomer gas.

3. Consider sponsoring a research program in the U.S. to confirm and to provide additional data in Dorter Viola's study area. The proposed program would cost approximately $100,000 per year.

The meeting attendance was light with about 30 people present. A full list of those attending will be issued later by MCA.

Continuation of the Acroosteolysis Registry Program was estimated to cost $300 to $500 per month, depending on the case load. The program has cost $1,000 for eighteen months operation to date. A firm budget for future operation was not available at this time.

URL 11699

Essentially all those present expressed a desire to continue the program now supported by about ten companies. Individual companies will be contacted for further authorization of funds. Union Carbide should continue to participate in this program at least until the physiological effects of vinyl chloride are better defined.

Dr. P. L. Viola, et al of the Regina Elena Institute for Cancer, Research, Rome, Italy, sponsored by Solvay M-C, started out to study acroosteolysis and its attendant Raynaud's phenomena. He originally started working with monkeys and later switched to rats because of cost and other factors. Doctor Viola exposed rats to varying concentrations of acetylene derived vinyl chloride and noted the following incidence of tumors:

Vinyl Chloride Concentration	Incidence of Tumors
30,000 ppm	65%
20,000 ppm	60%
10,000 ppm	25%
5,000 ppm	10-15%
<5,000 ppm	Some tumors

(Dr. M. J. LaFevre, Solvay M.C., stated later that the incidence of tumors in control groups of this strain of rats was 5%.)

Doctor Viola's initial work involving exposure of rats to 30,000 ppm VC was reported at the Tenth International Cancer Congress, Houston, Texas in May 1970 and was later published in Cancer Research, May 1971. The remaining data is unpublished at this time. After the appearance of Doctor Viola's paper at the Houston meeting interested companies, including UCC, paid Doctor Viola's expenses for a meeting in Washington on May 5, 1971.

Publishing of Doctor Viola's work in the U.S. could lead to serious problems with regard to the vinyl chloride monomer and resin industry. These are as follows:

1. The Delaney Amendment bans the use of any material in food that can cause cancer.

2. A law exists in Pennsylvania banning carcinogens from the air; i.e., the allowable threshold limit is zero.

3. The present political climate in the U.S. is such that a campaign by Mr. R. Nader and others could force an industrial upheaval via new laws or strict interpretation of pollution and occupational health laws.

There has been no Government reaction to Viola's work, to date. The ACGIH plans to discuss it this week at their meeting.

Dr. T. R. Torkleson reviewed the proposed MCA-sponsored animal study. This program involved exposure of rats and mice to three levels of vinyl chloride gas concentration - 5,000, 1,400, and 500 ppm. The vinyl chloride would be derived from ethylene and from acetylene. The rat study would cover 24 months while the mouse study would cover 12 months. The cost of the study was estimated to be $183,000 by Industrial Biotest, Chicago, Illinois.

Depending on the results of this study, an epidemiological study of the industry could be required. If vinyl chloride were exonerated in the proposed animal study, then a study of the effects of the material on progeny might be required.

The need for two sources of vinyl chloride and the chosen exposure concentrations was questioned, but no action was taken at this time.

Dr. M. J. LeFevre, Solvay M. C., discussed the work of his Company in Europe as well as his own knowledge regarding physiological effects of vinyl chloride. Items of interest are as follows:

1. Rumanian work showed 10% liver enlargement as well as acroosteolysis. Workers in Spain showed unnatural weariness, possibly indicating liver involvement. This was not noted in French or Belgian workers.

2. Doctor Viola found 28 impurities in his vinyl chloride including methyl chloride. This could be a major factor.

3. The bone tumors noted by Viola were probably acroosteolysis. Doctor LaFevre has seen lesions in the knees and in the pelvic area of the back.

4. No acroosteolysis has been found in monomer and compound plant workers. No tumors in reactor cleaners at Solvay M.C. plants.

5. Doctor LaFevre theorizes that vinyl chloride is absorbed in body fats and is carried to the brain. It acts on the centers controlling circulation of blood to the extremities. Restriction of the blood flow causes the pH of the bone structures to move from a normal basic condition where minerals are deposited to an acidic condition causing removal of minerals from the bones. Acroosteolysis is caused by general exposure and inhalation of vinyl chloride; not just exposure of the hands.

6. Doctor Viola's work is being checked and expanded. European studies underway involve exposure of animals to concentrations of 20,000, 10,000, 5,000, 2,000, 500, and perhaps 100 ppm. Vinyl chloride used will be a mixture of 50% acetylene and 50% ethylene derived.

The afternoon discussion originally planned to organize industry support for the MCA program showed that many questions existed and would have to be answered before a program could be presented for industry support. Some of the principal items discussed were:

1. Acetylene-based vinyl chloride monomer could possibly be cut from the study except to confirm Doctor Viola's work at the 5,000 ppm exposure level.

2. Lower concentration exposure levels, such as 50 ppm, should be checked.

3. The animal study proposal was still not completely set and it should not overlap the European study mentioned by Doctor LaFevre.

4. Human epidemiological studies should be made.

5. All industry sponsors should pay their pro rata share, but what is a pro rata share?

6. The Government should sponsor the study. Even if unfavorable, they wouldn't shut down an industry of this size.

7. Vinyl chloride monomer is full of impurities, and one of these must be a carcinogen.

When it became evident that more study was required, an industry subcommittee was appointed to study the problems and make recommendations to the Occupational Health Committee of MCA. The committee consists of:

R. K. Wheeler, Jr., Chairman
Union Carbide Corporation

Norman C. White, M. D.
Shell Chemical Company

M. V. Anthony
Stauffer Chemical Company

The Committee is to seek opinions and data from industry members and to meet with Dr. K. D. Johnson, MCA Assistant Technical Director, Occupational Health, on December 14, 1971 to prepare a program. The Committee is to recommend a program industry will support and recommend procedures for funding the program. Questions of study scope, acetylene vs ethylene derived vinyl chloride, and significant impurities in vinyl chloride will be resolved.

The MCA will survey members of the industry regarding their willingness to support a $100,000 per year study with costs allocated to sponsors based on published capacities of monomer and polymer. Monomer producers will be asked for representative analyses of their monomer and their methods of analysis.

Assuming 100% industry participation, Union Carbide's share of the program cost should be approximately $5,000 per year. This cost should be either borne directly by the Corporation or charged to Vinyl Resins, Dynel, and Fluorocarbon profit centers on the basis of their vinyl chloride consumption.

Union Carbide's general support for the NCA's program has been pledged, based on the following:

1. The industry has a responsibility to its employees and customers to take any necessary action to protect them. Union Carbide Corporation is a responsible member of that industry and will bear its share of the cost.

2. Union Carbide has a large stake in the areas most likely to be affected such as food, food packaging, fibers, and aerosols and would be seriously hurt by arbitrary or panic-induced government restrictions.

3. Union Carbide has a plethora of knowledge and experience that can add to the success of the proposed study and that can guide such a study to reasoned conclusions.

R. N. Wheeler, Jr.

RNWJr/ra

URL 11704

CANCEROGENIC EFFECT OF VINYL CHLORIDE

P. L. Viola

(Regina Elena Institute for Cancer Research)
Rome, Italy

Presented at the Tenth International Cancer Congress
Houston, Texas May 22-29, 1970

Cancerogenic Effect of Vinyl Chloride
P. L. Viola

Tumors of the respiratory tract

Even if as far as the percentage is concerned these occur in a smaller number, their anatomic appearance is mainly of an adenocarcinoma; only in [illegible] has been observed a tumor of the epidermoid type. [illegible] tumor showed an early developmental stage and consisted predominently of cubic or columnar cells arranged as [illegible] of irregular tubular and papillary elements supported by poorly developed fibrous stroma.

Tumors of the bones

In the metaphysical region of the four limbs a large proliferation of cartilaginous tissue arises outwardly to the periostium and seems to derive directly out of the osseous cortical by the growth of its cells. The cartilagenous growth is dishomogeneous as it is shown by the extension of finger-like prolongations into the boundary of neoformed tissue. Beside the chondroblastic, chondrocytic and angiomatous areas, manifestation of noticeable growth power, there are cartilaginous zones with regressive features, as fibrosis and hyalinosis.

The results reported above indicated that vinyl chloride is an effective carcinogenic agent for the rat. As for many carcinogenesis studies, where multiple tumors arise at different sites, in different tissues and organs, the data obtained need to be evaluated considering a more prompt positive response according to the ideal concentration of the carcinogenic. It is noteworthy to emphasize that the cutaneous system represents an impressive pattern of susceptibility to the vinyl chloride. Another point to be considered is that all the cutaneous tumors developed in the same site, i.e., the region including the area in which submaxillary and parotid gland are located.

No implications to human pathology can be extrapolated from the experimental model reported in this paper.

[CANCER RESEARCH 31, 516–522, May 1971]

Oncogenic Response of Rat Skin, Lungs, and Bones to Vinyl Chloride[1]

P. L. Viola, A. Bigotti, and A. Caputo

Regina Elena Institute for Cancer Research, Rome, Italy

SUMMARY

Rats (Ar/IRE Wistar strain) exposed for 12 months to vapors of vinyl chloride developed tumors of the skin, lungs, and bones. The cutaneous tumors, which always appeared in the area in which submaxillary and parotid glands are located, have been histologically recognized as epidermoid carcinomas, papillomas, and mucoepidermoid carcinomas. The morphological characteristics of lung tumors, which occurred in a lower percentage, were mainly of the adenocarcinoma type, with the exception of a single epidermoid tumor originating from the epithelial covering cells. In a minor number of rats, a large proliferation of cartilaginous tissue diagnosed as osteochondroma developed in the metacarpal and metatarsal regions of the four limbs.

INTRODUCTION

The oncogenic properties of some chemical organic compounds used for the preparation of "plastics" have been widely investigated, and their limits and effectiveness have been well established. Detailed information on this subject may be found in the literature (5, 6, 8); however, all information and references are exclusively related to highly polymerized compounds of roughly the same size as used in various industries.

Oncogenic polymers produce sarcomatous tumors, with the exception of polyurethans which, as reported by Hueper (6), also induce adenocarcinomas. Recently, it has been demonstrated that sarcomatous tumors (1–4, 7) are transplantable, and it has been suggested that they may originate from the tissues of the capsule that gradually covers the plastic film. Thus, Brand *et al.* (2–4) have observed premalignant areas made of poorly differentiated fibroblasts which were firmly attached to the plastic film up to the moment of malignant transformation.

This investigation demonstrates that even the monomer vinyl chloride possesses oncogenic properties when used with an appropriate model different from the models previously reported by several authors (9–12). The carcinogenic response to vinyl chloride follows a singular pattern for the different tissues and organs of the rat.

MATERIALS AND METHODS

The experiments were performed with vinyl chloride (CH_2=$CHCl$, the monohalogenate derivative of ethylene) of commercial grade (99% purity) assumed to contain insignificant amounts of various noncarcinogenic contaminants.

Three-month-old Wistar (Ar/IRE) male albino rats (about 150 g body weight) were exposed to vinyl chloride vapors for 4 hr a day, 5 days a week, for 12 months. The animals were kept in metal or plastic, air-tight cages in which a constant flow of air, containing 3% v/v (equal to 30,000 ppm) of vinyl chloride, was introduced. Twenty-five rats of the same strain were the control group. At the end of the treatment, the surviving animals were killed at 20-day intervals, and the most important tissues and organs were examined histologically by standard methods. During the period of exposure, the animals were slightly soporific; however, the first few months of treatment were well tolerated and no changes in growth or behavior were noticed. After 10 months of treatment, some animals began to show a hard mass in the parasauricular region which became progressively larger until it reached the size of a walnut or slightly larger. In most cases, the swelling was unilateral; it was bilateral in only a few animals. After 12 or 13 months, the growing masses became ulcerated and discharged necrotic debris, while a certain amount of tumorous tissue began to form on their surfaces. In addition, we observed that the masses were an integral part of the parasauricular region and could not be distinguished from the local tissues. Caseous necrotic zones were found. Pleura and pericardium often showed diffuse inflammation of a fibrous nature and, in many cases, the lungs were covered with a number of white formations as large as grains of rice or even larger and harder than the lungs themselves. In 2 cases, the lungs were hemorrhagic with milky, thick fluid in the pleural cavities. The liver was sometimes increased in size and very fragile. The animals were subjected to X-ray analyses at different intervals from the beginning of treatment in order to control the state of the skeletal bones.

All the animals that inhaled vinyl chloride showed a series of parenchymal lesions. Among these, most prominent was the disappearance of granular and Purkinje cells, degenerat

[1] A preliminary report of the results reported here was given at the Tenth International Cancer Congress, Houston, Texas, May 22–24, 1970.

Received July 31, 1970; accepted January 12, 1971.

of the cerebellum, severe chronic hepatitis, interstitial pneumonia, and moderate swelling of the kidney parenchyma, often assuming the pattern of tubulonephrosis.

RESULTS

The rates of survival and the main findings are summarized in Table 1. Almost all the animals developed tumors of the skin and lungs. Very few animals developed bone tumors; in these cases, the tumors were localized in the metacarpal and metatarsal bones of all 4 extremities. Skin tumors were by far the most frequent, amounting to 65 or 70%.

Skin Tumors. The tumor that developed most frequently in the parauricular region was the epidermoid carcinoma, but we also observed papillomas and rarely mucoepidermoid carcinomas. In all cases, the neoplasms were of epithelial nature. The 3 patterns noticed cannot be compared to various histotypes but rather to a transition of one type into the other or, and which is more likely, to different stages of the same proliferative type.

Warty subauricular growths occurred in some rats. The histological picture showed papillar epithelial proliferation, with progressive increase in the thickness of the epidermis (*Fig. 1*).

The papillary warts of exophytic type had a fibrous vascular stroma and various degrees of inflammatory lymphocytic infiltration, marked hyperkeratosis, parakeratosis, acanthosis, and areas of individual dyskeratosis or pearl-like horny formations.

The epithelial cells of the penetrating columns (Fig. 2) were irregularly arranged and were frequently accompanied by an inflammatory infiltration of the dermis. The typical features of the Malpighian layer and of the stratum corneum of the prickle cells and of germinal layers were easily recognized (Fig. 3). The horny layer was composed largely of cell nests, which appeared at certain points within the epithelial masses and assumed the well-known appearance of "horny pearls" (Fig. 3, *arrows*); they were made of flattened and compressed prickle cells without nuclei and were located around a central core of keratin.

Table 1

Oncogenic effects of inhaled vinyl chloride as a function of time

The animals were exposed to vinyl chloride vapors for 4 hr a day, 5 days a week, for a total of 12 months, in a constant flow of air containing 3% v/v vinyl chloride.

Rat	Survival rate	Tumors		
		Skin	Lungs	Bones
1	300	Mucoepidermoid carcinoma	Adenoacanthoma	Osteochondroma
2, 3	280–300	Epidermoid carcinoma, keratinizing type	No tumor	No tumor
4	310	Epidermoid carcinoma, keratinizing type	Adenocarcinoma	No tumor
5	333	Papilloma, keratotic type	No tumor	Osteochondroma
6	337	Epidermoid carcinoma	No tumor	Osteochondroma
7	347	Epidermoid carcinoma	No tumor	No tumor
8	347	Mucoepidermoid carcinoma	No tumor	Osteochondroma
14	354	Epidermoid carcinoma	No tumor	No tumor
16, 17	359	Epidermoid carcinoma	Adenocarcinoma	No tumor
21	380	Epidermoid carcinoma	No tumor	No tumor
22	380	Epidermoid carcinoma	Adenocarcinoma	Osteochondroma
23	380	Epidermoid carcinoma	No tumor	No tumor
24	380	Epidermoid carcinoma	Mucus-producing adenocarcinoma (alveolar cell carcinoma?)	No tumor
25	380	Epidermoid carcinoma	No tumor	No tumor
26	380	Epidermoid carcinoma	Squamous cell carcinoma	No tumor

Keratinization was irregular and often parakeratosis was observed in the areas of the tumor in which the cells were loosely aggregated and undergoing an individual rather than a collective type of keratinization (Fig. 4). In dyskeratotic areas, a few epithelial cells tended to form pearls. The tumor seldom showed an undifferentiated growth with cellular pleomorphism and several mitotic figures (Fig. 5). A few tumors showed little nests of isolated pale cells (Figs. 6 and 7) of 3 types: mucin-producing cells (originating from the duct epithelium of sweat glands or salivary glands); squamous cells; and intermediate cells with minor tendencies towards differentiation.

Respiratory Tract. These tumors, although occurring rarely, were mainly adenocarcinomatous. Only in 1 rat did we observe an epidermoid tumor originating from the epithelium-covering cells. Sometimes, the tumors were seen in their early development and consisted predominantly of cubic or columnar cells arranged as regular or irregular tubular and papillary elements (Fig. 8) and supported by poorly developed fibrous stroma (Fig. 9).

In other cases, glandular structures were often imperfectly formed and appeared as sheet-like proliferations of undifferentiated or pleomorphic character. The cells showed a tendency to extend into the pulmonary parenchyma, thus simulating the microscopic features of the so-called alveolar cell carcinoma (Fig. 10). Sometimes, this was the prevailing pattern. The pulmonary air sacs were limited by 1 or more layers of cubic, columnar, or polyhedral cells with abundant cytoplasm that was faintly eosinophilic (Fig. 11); frequently, adenopapillary excrescences spreading into the alveolar spaces were present.

In some areas, foci of cellular polymorphism with hyperchromatic nuclei were noticed; mucin was produced in varying amounts and secreted into the lumen of the tubules and acini. There were small pools of mucin in which signet ring cells occurred, either alone or in small clusters (Fig. 12). The alveolar walls were often quite thick and, at times, showed an inflammatory infiltration.

As mentioned before, a single tumor showed squamous structures and appeared to have been formed mainly by spindle and oval undifferentiated cells (Fig. 12).

Bones. In the metacarpal and metatarsal regions of the 4 limbs, a large proliferation of cartilaginous tissues arose outward from the periosteum and, from the appearance of its cells, seemed to derive directly from the cortical bone (Fig. 14). The periosteum also grew and in some areas spread as finger-like prolongations into the newly formed cartilage (Fig. 15). In these places, a gradual transition between fibrous cartilage, periosteum, and bone could be noticed.

The newly formed cartilage appeared irregular with atypical areas; the cells, which had nuclei larger than the normal chondrocytes, lay in well-formed, capsulated lacunae. The cells occurred singly, in pairs, or in tetrads and, although of different size and shape, they usually contained a single, darkly stained nucleus. The cartilaginous growth was not homogeneous, as shown by the extension of the finger-like prolongations into the boundary of newly formed tissue. Besides the chondroblastic, chondrocytic, and angiomatous areas which indicated a rapid growth, there were also cartilaginous zones possessing regressive features, such as *fibrosis and hyalinosis*. The perichondrium appeared often as a compressed and structurally altered fibrous tissue.

In some cases, the tumor growth was related to the stage of the endochondral ossification occurring below the "epiphysial plate." Ossification was irregular, so that osseous trabeculae varied greatly in thickness and contours. In other cases, foci of active cellular proliferation, cartilaginous areas, chondroid developmental nests, and calcified bones occurred in the deeper portions of the trabeculae (Fig. 18).

The new formation appeared to be an osteochondroma and consisted essentially of a bony protuberance capped by cartilage and a fibrous layer, which represented the perichondrium.

The fibrous layer was continuous with the periosteum of the adjacent cortical bone and extended inward to form septa separating and enclosing lobules of cartilage.

Control Animals. The control rats were kept under the same conditions as the experimental rats and at the appropriate time were subjected to a constant flow of air without vinyl chloride. None of these animals developed tumors or the types of parenchymal lesions developed by the rats that inhaled vinyl chloride. In a very few of the control rats, there was a swelling of the liver and kidneys.

DISCUSSION

As in many carcinogenesis studies in which multiple tumors arise in different tissues and organs, the data must be evaluated in terms of a more prompt positive response to be obtained with the ideal concentration of the carcinogenic compound. The cutaneous system is the most susceptible to the oncogenic effects of vinyl chloride.

Our experimental data do not explain why the cutaneous tumors developed in the same site, *i.e.*, the region including the area in which the submaxillary and parotid glands are located. It is possible that the salivary glands may by involved in the concentration or excretion of vinyl chloride or some of its active decomposition products. This hypothesis is strongly supported by morphological findings showing the special tendency of the developed tumor to appear as a mucoepidermoid carcinoma, which indicates the active contribution of the mucus glandular cells to the tumoral growth. Such kinds of histotypes are often related to some glandular aggregates, and, therefore, the histogenesis of human mucoepidermoid carcinoma has been restricted to the cells of intercalated ducts. This hypothetical interpretion must be confirmed by future experiments in which the action of the vinyl chloride should be restricted to the salivary system. In the concentrations used, saturation and wetting of the fur might well be expected. Under these circumstances, the natural cleansing habit of the rat might add a significant ingestion problem with subsequent concentration of vinyl chloride in the salivary glands. The local excessive concentration could be the result of the difficulty of complete cleansing by the rat.

The neoplastic response of the lower respiratory tract, although of lesser magnitude, is of relevant interest, since it

of the tumors were morphologically similar to those described of the skin. The hypothesis that mucus-producing cells may capable of retaining vinyl chloride or its decomposition oducts seems to be relevant once more. Obviously, a fferent interpretation is required for the pathogenesis of the se tumors and for their simultaneous incidence at the level ll 4 limbs.

FERENCES

Banerjee, M., and Bates, R. Prevalence of Heteroploidy in Plastic Film-induced Primary Sarcomas. Brit. J. Cancer, *20:* 555–563, 1966.

Brand, G., and Bueen, L. Polymer Tumorigenesis: Multiple Preneoplastic Clones in Priority Order with Clonal Inhibition. Proc. Soc. Exptl. Biol. Med., *128:* 1153–1158, 1968.

Brand, G., Bueen, L., and Brand, I. Malignant Transformation and Maturation in Non-dividing Cells during Polymer Tumorigenesis. Proc. Soc. Exptl. Biol. Med., *124:* 675–678, 1967.

Brand, G., Bueen, L., and Brand, I. Carcinogenesis from Polymer Implants: New Aspects from Chromosomal and Transplantation Studies during Preneoplasia. J. Natl. Cancer Inst., *39:* 663–679, 1970.

Druckrey, H. Experimentelle Beitraege zum Mechanismus d. Carcinogenen Wirkung. Arzneimittel-Forsch., *1:* 383–395, 195

Hueper, W. C. Cancer Induction by Polyurethan and Polysilicor Plastics. J. Natl. Cancer Inst., *33:* 1005–1027, 1964.

Johnson, K., Bueen, L., Brand, I., and Brand, G. Polym Tumorigenesis Clonal Determination of Histopathologic Characteristics during Early Preneoplasia: Relationships I Karyotype, Mouse Strain, and Sex. J. Natl. Cancer Inst., *4* 785–793, 1970.

Kogan, A. Experimental Blastomogenesis Caused by Synthet Polymers (Plastics). Meditsina, Moscow, *1:* 215–237, 1965.

Mastromatteo, E., Fisher, A. M., Christi, H., and Danziger, E Acute Inhalation Toxicity of Vinyl Chloride to Laborator Animals. Am. Ind. Hyg. Assoc. J., *21:* 394–397, 1960.

Torkerson, T. R., Oyen, F., and Rowe, V. K. The Toxicity of Viny Chloride as Determined by Repeated Exposure of Laborator Animals. Ind. Hyg. J., 354–361, October 1961.

Van Duren, B. L., Sivak, A., Goldschmidt, B. M., Katz, C., an Melchionne, S. Carcinogenicity of Halo-Ethers. J. Natl. Cance Inst., *41:* 481–486, 1969.

Viola, P. L. Pathology of Vinyl Chloride. 16th Internationa Congress of Occupational Health. (Communication No. 38) Tokyo, 1969.

1 to 18. All sections were stained with H & E.

1. Squamous cell papilloma of the skin. × 25.

2. Transitional stage from papilloma to infiltrative type of cancer. × 80.

3. Finger-like trabeculae branch to form secondary processes showing horny pearl formation (*arrows*). × 25.

4. Dyskeratotic area. Few epithelial cells with a tendency to form whorls. Little capacity to develop into horny pearls. × 250.

5. Atypical cells partly lacking prickles and showing considerable variation in size, shape and many mitotic figures. × 250.

6. Mucoepidermoid skin tumor. Occurrence of hydropic epidermoid cells, basal cells, columnar cells, and oxyphilic cells in vario forms. × 100.

7. Mucoepidermoid skin tumor, showing differentiation of masses of squamous epithelium from columnar cells, lining and proliferating in dilated tubular spaces. × 100.

8. Micronodular adenocarcinoma of the lung arising from a segmental bronchus. × 25.

9. Detail of Fig. 8 showing tubular aggregates made up by cells with hyperchromatic nuclei.

10. Nodular bronchiolar alveolar mucus-secreting adenocarcinoma. × 100.

11. Detail of Fig. 10, showing an alveologenic pattern. × 250.

12. Mucus-producing cells with hyperchromatic and pleomorphic nuclei and occurrence of signet ring cells. × 250.

13. Squamous cell carcinoma of the lung. × 100.

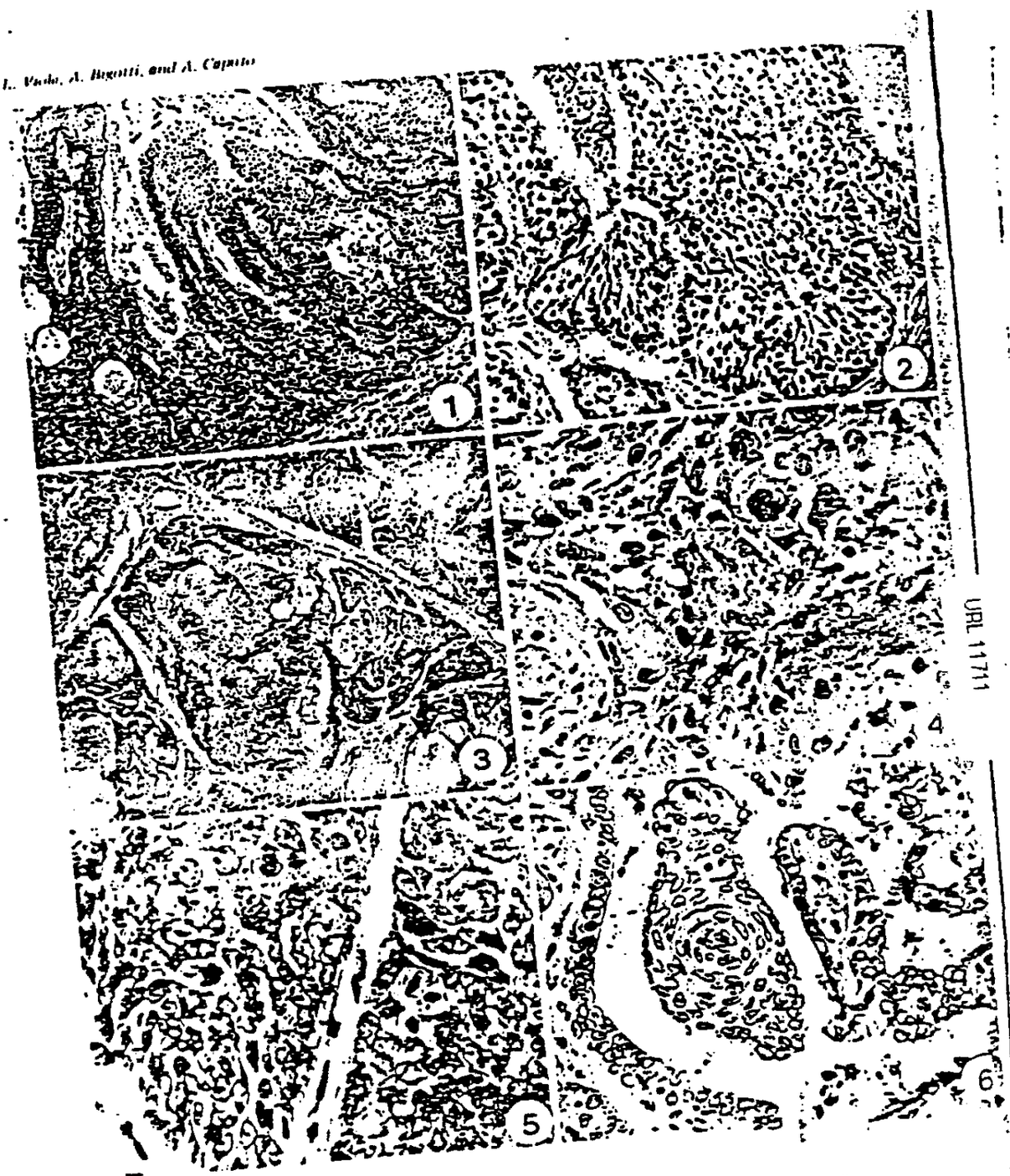
14. Osteochondroma developing as a protuberance from the small bones of metacarpus and metatarsus. × 25.

15. Magnification of Fig. 14. The protuberance consists of bone trabeculae, capped by cartilage, and a fibrous layer functioning as periosteum. × 100.

16. Osteochondroma. Cartilaginous growth characterized by finger-like proliferation. × 100.

17. Osteochondroma. Area of endochondrial ossification. × 100.

18. Cellular area of an osteochondroma showing the transition from cartilage to osteoid. × 100.



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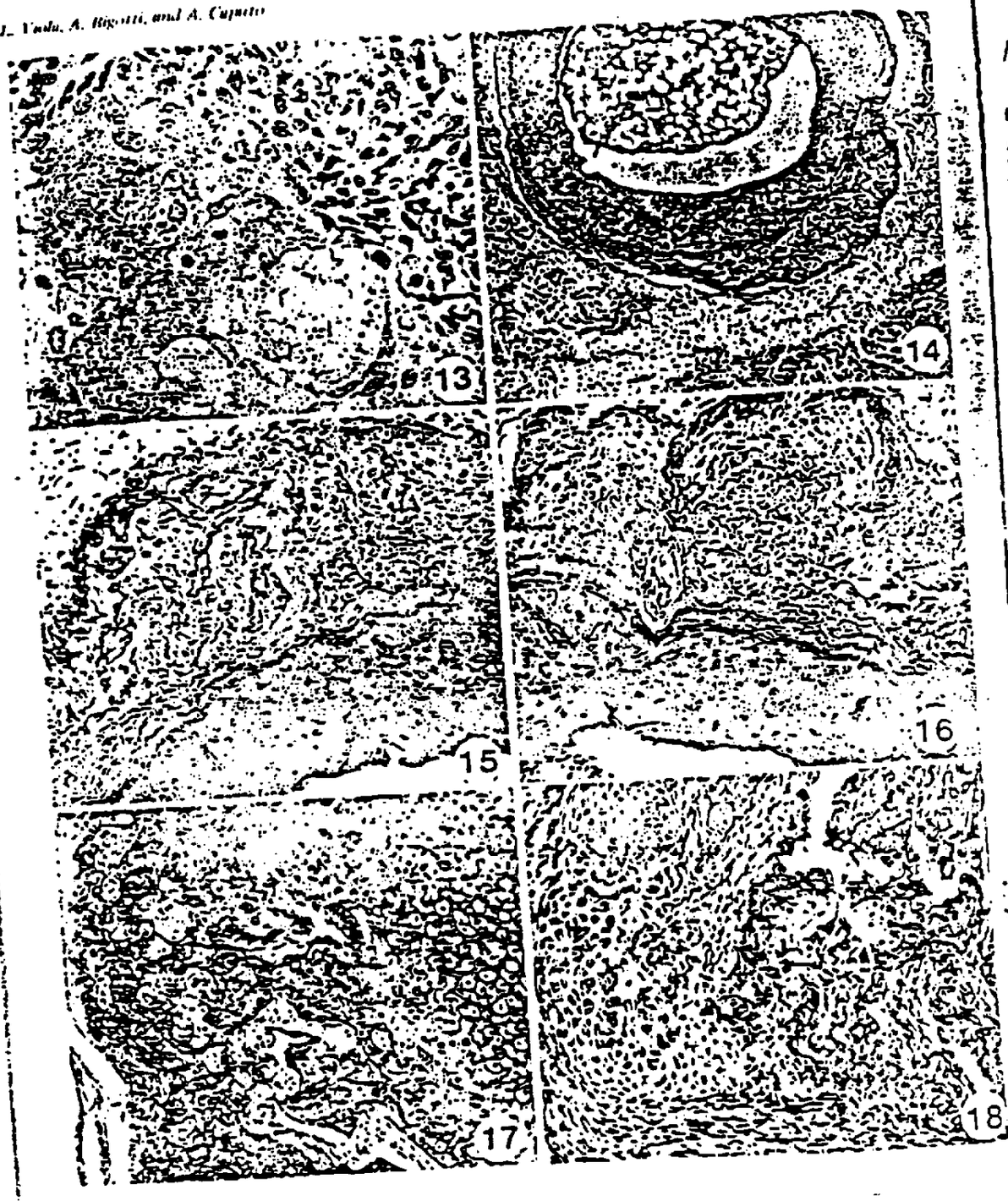
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CURRICULUM VITAE Ex. 1 Prof. Doll 7/26/88 CAEA.

RICHARD DOLL

BORN	28 October, 1912
GRADUATED	St. Thomas's Hospital Medical School, University of London, M.B., B.S., 1937
OTHER DEGREES	M.D., London, 1945 D.Sc., London, 1958 D.M., Oxford, 1969
HONORARY DEGREES	D.Sc., Newcastle 1969; Belfast 1972; Reading 1973; Newfoundland 1973; D.M., Tasmania 1975.
PROFESSIONAL AWARDS	F.R.C.P. London, 1957; Honorary F.R.C.G.P., 1978. F.R.S., 1966. Honorary member of the American Association for Cancer Research, the American Gastroenterological Association, the American Epidemiological Society, the American Academy of Arts and Sciences, the Italian Oncological Society, and the Norwegian Academy of Sciences.
HONOURS	Kt. 1971 O.B.E. 1956
MILITARY SERVICE	R.A.M.C. 1939-45: Battalion Medical Officer, France, 1939-40, Medical Specialist Middle East, 1941-44.
POSTS HELD	Casualty Officer and House Physician, St. Thomas's Hospital, 1938-39. House Physician, Royal Postgraduate Medical School, Hammersmith, 1939. Junior Assistant, Medical Unit, St. Thomas's Hospital, 1945. Research Assistant to Dr Avery Jones, Central Middlesex Hospital, 1946-47. Member MRC's Statistical Research Unit, 1948-69 Deputy Director " " 1956-60 Director " " 1961-69 Deputy Director of MRC's Clinical Research Centre, 1966-69. Honorary Associate Physician, Central Middlesex Hospital, 1949-69. Honorary Lecturer in Epidemiology, London School of Hygiene and Tropical Medicine, 1956-62, and University College Hospital Medical School, 1962-69.

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POSTS HELD

Regius Professor of Medicine, University of Oxford, and Honorary Physician, Radcliffe Infirmary, 1969-79.

Honorary Director, Imperial Cancer Research Fund's Cancer Epidemiology and Clinical Trials Unit, 1978-83.

Warden, Green College, Oxford, 1979-83.

PRESENT POST

Acting Director, Imperial Cancer Research Fund's Cancer Epidemiology and Clinical Trials Research Unit.

AWARDS

William Julius Mickle Fellow, University of London, 1955.
David Anderson Berry Prize, Royal Society of Edinburgh (jointly, with W.M. Court Brown), 1958.
Bisset Hawkins Medal, Royal College of Physicians, 1962.
United Nations Award for Cancer Research, 1962.
Gairdner Award, Toronto, 1970.
Buchanan Medal of the Royal Society, 1972.
Nuffield Medal, Royal Society of Medicine, 1973.
Presidential Award, New York Academy of Sciences, 1974.
Prix Griffuel, Paris, 1975.
John Snow Award, Epidemiology Section, American Public Health Association, 1976.
Gold Medal, Royal Institute of Public Health, 1977.
Charles, S. Mott Prize for Cancer Reserch, New York, 1979.
Gold Medal, British Medical Association, 1983.
Wilhelm Conrad Röntgen Prize, Accademia dei Lincei, Rome, 1984.
Johann-Georg-Zimmermann Preise, Hannover, 1985.
Founders' Award, Chemical Industry Institute of Toxicology, 1986.
Royal Medal, The Royal Society, 1986.

COMMITTEES

Chairman, Management Committee, Institute of Cancer Research, 1978 to date.
Member, Council of Institute of Occupational Medicine, 1981 to date.
Chairman, Medical Research Council's Cancer Coordinating Committee, 1973-77.
" Adverse Reactions Sub-Committee of the Committee on Safety of Medicines, 1970-77.
Sometime member, Royal Commission on Environmental Pollution.
" Commission on Energy and the Environment.
" Council of the Royal Society.
" Medical Research Council.
" Council of the Royal College of Physicians.
" Advisory Committee on Medical Research, World Health Organization.
" Scientific Council of the International Agency for Research on Cancer.
" Council of the International Union against Cancer.

LIST OF PUBLICATIONS

RICHARD DOLL

1936 1. DOLL, R. (1936). Medical statistics. St Thomas's Hospital Gazette, 294-297

1937 2. DOLL, R. (1937). Notes on the Berger rhythm and the electro-encephalogram. St Thomas's Hospital Gazette, 157-159

1939 3. RICHARDSON, J.S. and DOLL, R. (1939). The juvenile form of the adreno-genital syndrome. Brit. med. J., 1, 501

1946 4.* DOLL, R. (1946). Helium in the treatment of asthma. Thorax, 1, 30-38

1948 5.* DOLL, R. and SCHNEIDER, R. (1948). The effect of paludrine on human gastric secretion. Brit. J. Pharmacol. & Chemo., 3, 352-353

1949 6. DOLL, R. and JONES, F.A. (1949). Environmental factors in the aetiology of peptic ulcer. The Practitioner, 162 44-50

7. DOLL, R. and BUCKATZSCH, M.M. (1949). Sickness absence due to peptic ulcer. Brit. J. industr. Med., 6, 100-102

8. DOLL, R., JONES, F.A. and MACLAGAN, N.F. (1949). Gastric secretion and subsequent dyspepsia. Lancet, 2, 984

1950 9.* BISHOP, P.M.F., RICHARDS, N.A. and DOLL, R. (1950). Habitual abortion. Brit. med. J., 2, 130

10. DOLL, R. (1950). Occupational factors in peptic ulcer. Medical Research Council, Proceedings of a Conference on Application of Scientific Methods to Industrial Medicine and Service Medicine. London, HMSO, pp.16-19

11. DOLL, R. (1950). Perforated carcinoma of the stomach simulating perforated gastric ulcer. Brit. med. J., 1, 215

12. DOLL, R. and HILL, A.B. (1950). Smoking and carcinoma of the lung. Brit. med. J., 2, 739

13.* DOLL, R. and BUCH, J. (1950). Hereditary factors in peptic ulcer. Ann. Eugenics, 15, 135-146

1950 contd 14. DOLL (1950). Peptic ulcer. Brit. Encyclopaed. med. Prac., 2, 504 (Interim Suppl.)

1951 15. JONES, F.A., DOLL, R., FLETCHER, C. and RODGERS, H.W. (1951). The risks of gastroscopy. Lancet, 1, 647

16. DOLL, R., JONES, F.A. and BUCKATZSCH, M.M. (1951). Occupational factors in the aetiology of gastric and duodenal ulcers. Med. Res. Council Spec. Rep. Ser. No. 276. HMSO, London

17.* DOLL, R. and KELLOCK, T.D. (1951). The separate inheritance of gastric and duodenal ulcers. Ann. Eugenics, 16, 231-240

18.* DAFF, M.E., DOLL, R. and KENNAWAY, E.L. (1951). Cancer of the lung in relation to tobacco. Brit. J. Cancer, 5, 1-20

1952 19. DOLL, R. (1952). Peptic ulcer: I. Endemiology. In: Modern Trends in Gastroenterology. London, Butterworth, p.361

20. DOLL, R. and PYGOTT, F. (1952). Factors influencing the rate of healing of gastric ulcer. Lancet, 1, 171

21. DOLL, R. (1952). Causes of death among gas-workers with special reference to cancer of the lung. Brit. J. industr. Med., 9, 180

22.* DOLL, R. and HILL, A.B. (1952). A study of aetiology of carcinoma of the lung. Brit. med. J., 2, 1271

23. BUCKATZSCH, J. and DOLL, R. (1952). An experimental factor analysis of cancer mortality in England and Wales, 1921-30. J. Hygiene, 50, 384-390

1953 24.* MRC WORKING PARTY OF ANTIBIOTICS CLINICAL TRIALS COMMITTEE (incl. R. DOLL) (1953). Antibiotic and chemotherapeutic agents in the treatment of infantile diarrhoea and vomiting. Lancet, 2, 1163

25. JONES, F.A. and DOLL, R. (1953). Treatment and prognosis of acute perforated peptic ulcer. Brit. med. J., 1, 122

26. DOLL, R. (1953). Mortality from lung cancer among non-smokers. Brit. J. Cancer, 7, 303

27.* DOLL, R. (1953). Bronchial carcinoma: Incidence and aetiology. Brit. med. J., 2, 521-527 and 585-590

1953 contd 28. DOLL . (1953). Smoking and c' 'noma of the lung. Acta un. internat. contr. Cancer, 7, 495

1954 29. DOLL, R. (1954). The scientific approach. Ann. phys. Med., 2, 85

30. MRC COMMITTEE ON ANALGESIA (incl. R. DOLL) (1954). The use of trilene by midwives. Medical Research Council Memorandum No. 30. London, HMSO

31. TRUELOVE, S.C., WITTS, L.J., TUNBRIDGE, R.E., WATKINSON, G., JONES, F.A., DOLL, R., HARDY, T.L., ST JOHNSTON, C.R., CARD, W.I., WILSON, M. and TAYLOR, J. (1954). Cortisone in ulcerative colitis (preliminary report). Brit. med. J., 2, 375

32. DOLL, R. and PYGOTT, F. (1954). Clinical trial of Robaden and of cabbage juice in treatment of gastric ulcer. Lancet, 2, 1200-1204

33. DOLL, R. and HILL, A.B. (1954). The mortality of doctors in relation to their smoking habits. Brit. med. J., 1, 1451

34. DOLL, R. (1954). Cancer of the respiratory tract. Brit. J. industr. Med., 11, 305

35. ARMITAGE, P. and DOLL, R. (1954). The age distribution of cancer and a multi-stage theory of carcinogenesis. Brit. J. Cancer, 8, 1-12

36. BOYD, J.T. and DOLL, R. (1954). Gastro-intestinal cancer and the use of liquid paraffin. Brit. J. Cancer, 8, 231-237

1955 37. TRUELOVE, S.C., WITTS, L.J., TUNBRIDGE, R.E., WATKINSON, G., JONES, F.A., DOLL, R., HARDY, T.L., ST JOHNSTON, C.R., CARD, W.I., WILSON, M. and TAYLOR, J. (1955). Cortisone in ulcerative colitis (final report). Brit. med. J., 2, 1041

38. DOLL, R. (1955). Etiology of lung cancer. In: Advances in Cancer Research, 3. New York, Academic Press

39. DOLL, R. (1955). Mortality from lung cancer in asbestos workers. Brit. J. industr. Med., 12, 81-86

39A DOLL, R. (1955). Medical statistics. Middlesex Hospital Journal, 40, 190

1956 40. DOLL, , PRICE, R.V., PYGOTT, F and SANDERSON, P.H. (1956). Continuous intragastric milk drip in treatment of uncomplicated gastric ulcer. Lancet, 1, 70-73

41. DOLL, R., FRIEDLANDER, P. and PYGOTT, F. (1956). Dietetic treatment of peptic ulcer. Lancet, 1, 5-9

42.* HILL, A.B. and DOLL, R. (1956). Lung cancer and tobacco. Brit. med. J., 1, 1160

43. DOLL, R. and HILL, A.B. (1956). Lung cancer and other causes of death in relation to smoking. Brit. med. J., 2, 1071

44. DOLL, R. (1956). Environmental factors in the aetiology of cancer of the stomach. Gastroenterologia, 86, 320-328

1957 45. COURT BROWN, W.M. and DOLL, R. (1957). Leukaemia and aplastic anaemia in patients irradiated for ankylosing spondylitis. Med. Res. Council Spec. Rep. Ser. No. 295. London, HMSO

46. DOLL, R. and HILL, A.B. (1957). Deaths from poliomyelitis among British doctors. Brit. med. J., 1, 372

47. DOLL, R. (1957). Aetiology of cancer of the stomach. In: Modern Trends in Gastroenterology. London, Butterworth, pp.53-64

48.* DOLL, R., JONES, F.A., PYGOTT, F. and STUBBE, J.L. (1957). The risk of gastric cancer after medical treatment for gastric ulcer. Gastroenterologia, 88, 1

49. ARMITAGE, P. and DOLL, R. (1957). A two-stage theory of carcinogenesis in relation to the age distribution of human cancer. Brit. J. Cancer, 11, 161

50. DOLL, R. (1957). Lung cancer and smoking. Roy. Soc. Hlth J. 77, 247-254

51.* DOLL, R., HILL, A.B. and KREYBERG, L. (1957). The significance of cell type in relation to the aetiology of lung cancer. Brit. J. Cancer, 11, 43-48

1958 52.* DOLL, R. and JONES, F.A. (1958). Smoking and peptic ulcer. Allgemeine Pathologie und Bakteriologie, 21, 209-313

53. HILL, A.B., DOLL, R., GALLOWAY, T.McL. and HUGHES, J.P.O. (1958). Virus diseases in pregnancy and congenital defects. Brit. J. prev. soc. Med., 12, 1-7

1958 contd 54. COURT JWN, W.M. and DOLL, R. (. .). Expectation of life and mortality from cancer among British radiologists. Brit. med. J., 2, 181-187

55. DOLL, R. (1958). Cancer of the lung and nose in nickel workers. Brit. J. industr. Med., 15, 217-223

56. DOLL, R. (1958). Assessment of therapy for gastric ulcer by means of controlled clinical trials. Cs. gastroenterologi 12,22

57.* DOLL, R., JONES, F.A. and PYGOTT, F. (1958). Effect of smoking on the production and maintenance of gastric and duodenal ulcers. Lancet, 1, 657-662

1959 58.* DOLL, R., HILL, A.B., GRAY, P.G. and PARR, E.A. (1959). Lung cancer mortality and the length of cigarette ends: an international comparison. Brit. med. J., 1, 322-325

59. DOLL, R. (1959). Smoking and lung cancer: report to the sub-committee for the study of the risks of cancer from air pollution and the consumption of tobacco. Acta, 15, 1283

60.* DOLL, R. (1959). Lung cancer and cigarette smoking. Acta Un. internat. contr. Cancer, 15, 417

61. DOLL, R. (1959). Occupational lung cancer: a review. Brit. J. industr. Med., 16, 181-190

62.* DOLL, R. (1959). The concurrent assessment of several treatments. In: Controlled Clinical Trials. Oxford, Blackwell

63.* DOLL, R. (1959). Retrospective and prospective studies. In: Medical Surveys and Clinical Trials. Oxford University Press, pp.64-89

64.* DOLL, R. (1959). Cancer. In: Medical Surveys and Clinical Trials. Oxford University Press, pp.296-310

65. ARMITAGE, P., COURT BROWN, W.M. and DOLL, R. (1959). Dose-response relationship in radiation leukaemia. Nature, 184, 1669-1670

66. COURT BROWN, W.M. and DOLL, R. (1959). The expectation of life and cancer mortality of British radiologists. Progress in Nuclear Energy, Series VII, 2, 21-27 (Pergamon)

67. COURT BROWN, W.M. and DOLL, R. (1959). Adult leukaemia: trends in mortality in relation to aetiology. Brit. med. J. 1, 1063-1069

1960 68.* DOLL, (1960). The carcinogen' risk of radiation human leukaemia. Acta Un. internat. cancr. Cancer, 16, 418-421

69. COURT BROWN, W.M. and DOLL, R. (1960). Radiation hazards. In: Modern Trends in Occupational Health. London, Butterworth, pp.133-142

70. COURT BROWN, W.M., SPIERS, F.W., DOLL, R., DUFFY, B.J. and McHUGH, M.J. (1960). Geographical variation in leukaemia mortality in relation to background radiation and other factors. Brit. med. J., 1, 1753-1759

71. COURT BROWN, W.M., DOLL, R. and HILL, A.B. (1960). Incidence of leukaemia after exposure to diagnostic radiation in utero. Brit. med. J., 2, 1539-1545

72. DOLL, R., SWYNNERTON, B.F. and NEWELL, A.C. (1960). Observations on bloodgroup distribution in peptic ulcer and gastric cancer. Gut, 1, 31

73.* ARMITAGE, P. and DOLL, R. (1960). Stochastic models for carcinogenesis. In: Proc. 4th Berkeley Symposium on Mathematical Statistics and Probability, 4, 19. University of California Press

74. DOLL, R., HILL, A.B. and SAKULA, J. (1960). Asian influenza in pregnancy and congenital defects. Brit. J. prev. soc. Med., 14, 167-172

75. COURT BROWN, W.M., JACOBS, P.A. and DOLL, R. (1960). Interpretation of chromosome counts made on bone-marrow cells. Lancet, 1, 160-163

1961 76.* DOLL, R. and HANINGTON, E. (1961). International survey of eclampsia and pre-eclampsia, 1958-59: epidemiological aspects. Path. Microbiol., 24, 531-541 (7th International Conference of Society of Geographical Pathology, London)

77. COURT BROWN, W.M. and DOLL, R. (1961). Leukaemia in childhood and young adult life: trends in mortality in relation to aetiology. Brit. med. J., 1, 981-988

78.* MACKENZIE, A., DOLL, R., COURT BROWN, W.M. and SISSONS, H.A. (1961). Mortality from primary tumours of bone in England and Wales. Brit. med. J., 1, 1782-1790

79.* COURT BROWN, W.M., DOLL, R., HEASMAN, M.A. and SISSONS, H.A. (1961). Geographical distribution of primary tumours of bone in England and Wales. Brit. J. prev. soc. Med., 15, 167-170

1961 contd 80.*DOLL, DRANE, H. and NEWELL, A (1961). Secretion of blood group substances in duodenal and stomal ulcer, gastric carcinoma and diabetes mellitus. Gut, 2, 352

81. JACOBS, P.A., COURT BROWN, W.M. and DOLL, R. (1961). Distribution of human chromosome counts in relation to age. Nature, 191, 1178-1180

1962 82. DOLL, R. (1962). Age differences in susceptibility to carcinogenesis in man. Brit. J. Radiol., 35, 31-36

83. BUCKTON, K.E., JACOBS, P.A., COURT BROWN, W.M. and DOLL, R. (1962). Cancer subjects and abnormal cell division. Nature, 193, 591

84. DOLL, R. (1962). Susceptibility to carcinogenesis at different ages. Geront. clin., 4, 211-221

85. HOLLAND, W.W., DOLL, R. and CARTER, C.O. (1962). The mortality from leukaemia and other cancers among patients with Down's syndrome (mongols) and among their parents. Brit. J. Cancer, 16, 177-186

86. BUCKTON, K.E., JACOBS, P.A., COURT BROWN, W.M. and DOLL, R. (1962). A study of the chromosome damage persisting after X-ray therapy for ankylosing spondylitis. Lancet, 2, 676-682

87.*DOLL, R., HILL, I.D., HUTTON, C. and UNDERWOOD, D.J. (1962). Clinical trial of a triterpenoid liquorice compound in gastric and duodenal ulcer. Lancet, 2, 793-796

88.*DOLL, R. (1962). Information sought on somatic effects. In: The Use of Vital and Health Statistics for Genetic and Radiation Studies. United Nations Publication Sales No. 61. XVII.8., New York, pp.11-18

1963 89.*JACOBS, P.A., BRUNTON, M., COURT BROWN, W.M., DOLL, R. and GOLDSTEIN, H. (1963). Change of human chromosome count distributions with age: evidence for a sex difference. Nature, 197, 1080-1081

90.*MRC WORKING PARTY ON EVALUATION OF DIFFERENT METHODS OF THERAPY IN LEUKAEMIA (incl. R. DOLL) (1963). Treatment of acute leukaemia in adults: comparison of steroid therapy at high and low dosage in conjunction with 6-mercaptopurine. Brit. med. J., 1, 7-14

91.*DOLL, R. (1963). Investigation into cigarette smoking and atmospheric pollution in the aetiology of lung cancer. Methods of Information in Medicine, 2, 13-19

1963 contd 93. CAMPBELL, H., DOLL, R. and LETCHER, J. (1963). Incidence of thyroid cancer in England and Wales. Brit. med. J., 2, 1370-1373

*DOLL, R. (1963). Interpretations of epidemiologic data. Cancer Research, 23, 1613-1623

1964 94. INTERNATIONAL WORKING PARTY OF THE ORGANIZATION MONDIALE DE GASTRO-ENTEROLOGIE RESEARCH SUB-COMMITTEE (incl. R.DOLL) (1964). The epidemiology of gastro-intestinal cancer with special reference to causation. Gut, 5, 196-200

95. ACHESON, E.D. and DOLL, R. (1964). Dietary factors in carcinoma of the stomach: a study of 100 cases and 200 controls. Gut, 5, 126-131

96.*DOLL, R. (1964). Medical treatment of gastric ulcer. Scot. med. J., 9, 183-196

97. DOLL, R. and HILL, A.B. (1964). Mortality in relation to smoking: ten years' observations of British doctors. Brit. med. J., 1, 1399-1410 and 1460-1467

98. HAYHOE, F.G.J., QUAGLINO, D. and DOLL, R. (1964). The cytology and cytochemistry of acute leukaemias. Med. Res. Council Spec. Rep. Ser. No. 304. London, HMSO

99.*DOLL, R. (1964). Epidemiological observations on susceptibility to cancer in man with special reference to age. Acta Un. internat. contr. Cancer, 20, 747-752

100. BOYD, J.T. and DOLL, R. (1964). A study of the aetiology of carcinoma of the cervix uteri. Brit. J. Cancer, 18, 419-434

101. DOLL, R. (1964). Aetiology of cancer of the cervix uteri. In: Revista del Instituto Nacional de Cancerologia. UICC Symposium on Cancer of the Uterus, Mexico City, 1964, pp.358-367

102. COURT BROWN, W.M., DOLL, R. and HILL, A.B. (1964). Leukaemia in Britain and Scandinavia. Path. Microbiol., 27, 644-654 (8th Conference of the International Society of Geographical Pathology, Milan, 1963)

1965 103.* DOLL, , FISHER, R.E.W., GAMMON, J., GUNN, W., HUGHES, G.O., TYRER, F.H. and WILSON, W. (1965). Mortality of gasworkers with special reference to cancers of the lung and bladder, chronic bronchitis, and pneumoconiosis. Brit. J. industr. Med., 22, 1-12

104.* DOLL, R. (1965). Cancer: the possibilities. Brit. med. J., 1, 471-473

105. DOLL, R., HILL, I.D. and HUTTON, C.F. (1965). Treatment of gastric ulcer with carbenoxolone sodium and oestrogens. Gut, 6, 19-24

106.* DOLL, R. (1965). Clinical trials. In: Evaluation of New Drugs in Man. Proc. 2nd International Pharmacol. Meeting, Prague, 1963. Czechoslovak Medical Press, pp.159-164

107.* DOLL, R. (1965). The epidemiological picture. In: Current Research in Leukaemia. Ed. F.G.J. Hayhoe. London, Syndics of Cambridge University Press, pp.280-299

108.* PIKE, M.C. and DOLL, R. (1965). Age at onset of lung cancer: significance in relation to effect of smoking. Lancet, 1, 665-668

109.* LANGMAN, M.J.S. and DOLL, R. (1965). ABO blood group and secretor status in relation to clinical characteristics of peptic ulcer. Gut, 6, 270-273

110. COURT BROWN, W.M. and DOLL, R. (1965). Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis. Brit. med. J., 2, 1327-1332

111.* KNOX, J.F., DOLL, R. and HILL, I.D. (1965). Cohort analysis of changes in incidence of bronchial carcinoma in a textile asbestos factory. Ann. N.Y. Acad. Sci., 132, 526-535

112. ARMITAGE, P., DOLL, R. and PIKE, M.C. (1965). Somatic mutation. Brit. med. J., 1, 723

1966 113. HILL, I.D., DOLL, R. and KNOX, J.F. (1966). Mortality among asbestos workers. Proc. roy. Soc. Med., 59, 59-60

114.* DOLL, R. and HILL, A.B. (1966). Mortality of British doctors in relation to smoking: observations on coronary thrombosis. In: Study of Cancer and Other Chronic Diseases National Cancer Institute Monograph No. 19. Bethesda, Maryland

1966 contd 115. INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION COMMITTEE I (incl. R. DOLL) (1966). The evaluation of risks from radiation. Health Physics, 12, 239-302

116.* MRC WORKING PARTY ON THE EVALUATION OF DIFFERENT METHODS OF THERAPY IN LEUKAEMIA (incl. R. DOLL) (1966). Treatment of acute leukaemia in adults: comparison of steroid and mercaptopurine therapy, alone and in conjunction (2nd Report) Brit. med. J., 1, 1383-1389

117.* LANGMAN, M.J.S., DOLL, R. and WILSON, J. (1966). Plasma and salivary thiocyanate in gastric cancer. Gut, 7, 549-552

118.* DOLL, R. (1966). Cancer bronchique et tabac. Les Bronches, 16, 313-324

119. DOLL, R., PAYNE, P. and WATERHOUSE, J. (Eds) (1966). Cancer Incidence in Five Continents. UICC, Springer-Verlag, Berlin

120.* DOLL, R. (1966). Mechanism of carcinogenesis: evidence from epidemiological data. In: Fifteenth Yearbook for Cancer Research and Fight Against Cancer in the Netherlands. Amsterdam, Vereniging het Nederlands Kanker Instituut, pp.13-31. (Wassink Lecture given by R. Doll, October 1965)

1967 121. LANGMAN, M.J.S., DOLL, R. and SARACCI, R. (1967). ABO blood group and secretor status in stomal ulcer. Gut, 8, 128-132

122.* MEDICAL RESEARCH COUNCIL SUBCOMMITTEE (incl. R.DOLL) (1967). Risk of thromboembolic disease in women taking oral contraceptives: a preliminary communication to the Medical Research Council by a Subcommittee. Brit. med. J., 2, 355-359

123. DOLL, R. and COOK, P. (1967). Summarizing indices for comparison of cancer incidence data. Int. J. Cancer, 2, 269-279

124.* DOLL, R. (1967). Statistical approach to the evaluation and prediction of possible carcinogenic action of drugs. In: Potential Carcinogenic Hazards from Drugs. Ed. R. Truhaut UICC Monograph Series, Vol. 7. Springer-Verlag, Berlin, pp.53-58

125.* DOLL, R. (1967). Worldwide distribution of gastrointestinal cancer. In: Tumors of the Alimentary Tract. National Cancer Institute Monograph No. 25, pp.173-190

1967 126.*TILL, M., HARDISTY, R.M., PIKE, C. and DOLL, R. (1967). contd Childhood leukaemia in Greater London: a search for evidence of clustering. Brit. med. J., 3, 755-758.

127.*DOLL, R. (1967). Controlled clinical trials and their evaluation: introduction. In: Proc. IXth Int. Cancer Congress. UICC Monograph Series Vol. 10. Ed. R.J.C. Harris. Springer-Verlag, Berlin, pp.193-194

128. DOLL, R. (1967). Prevention of Cancer: Pointers from Epidemiology. Nuffield Provincial Hospitals Trust, London

129.*DOLL, R. (1967). The statistical approach to industrial lung cancer. In: Some Aspects of Carcinoma of the Bronchus and Other Malignant Diseases of the Lung (A Symposium held on 4 and 5 July 1966). Ed. D. Teare and J. Fenning. King Edward VII Hospital, Midhurst, pp.5-18

130. COURT BROWN, W.M., DOLL, R. and SMITH, P. (1967). Neoplasia in patients treated with X-rays for ankylosing spondylitis or metropathia haemorrhagica. In: Proc. IXth Int. Cancer Congress. UICC Monograph Series Vol. 10. Ed. R.J.C. Harris. Springer-Verlag, Berlin, pp.119-126

1968 131. BLACKBURN, E.K., CALLENDER, S.T., DACIE, J.V., DOLL, R., GIRDWOOD, R.H., MOLLIN, D.L., SARACCI, R., STAFFORD, J.L., THOMPSON, R.B., VARADI, S. and WETHERLEY-MEIN, G. (1968). Possible association between pernicious anaemia and leukaemia: a prospective study of 1,625 patients with a note on the very high incidence of stomach cancer.. Int. J. Cancer, 3, 163-170

132.*MRC WORKING PARTY FOR THERAPEUTIC TRIALS IN LEUKAEMIA (incl. R. DOLL) (1968). Chronic granulocytic leukaemia: comparison of radiotherapy and busulphan therapy. Brit. med. J., 1, 201-208

133.*SPEIZER, F.E., DOLL, R., HEAF, P. and STRANG, L.B. (1968). Investigation into use of drugs preceding death from asthma. Brit. med. J., 1, 339-343

134. SPEIZER, F.E., DOLL, R. and HEAF, P. (1968). Observations on recent increase in mortality from asthma. Brit. med. J., 1, 335-339

135. DOLL, R., LANGMAN, M.J.S. and SHAWDON, H.H. (1968). Treatment of gastric ulcer with carbenoxolone: antagonistic effect of spironolactone. Gut, 9, 42-45

136.*DOLL, R., LANGMAN, M.J.S. and SHAWDON, H.H. (1968). Treatment of gastric ulcer with oestrogens. Gut, 9, 46-47

contd of X irradiation in patients treated for metropathia haemorrhagica. Brit. J. Radiol., 1, 362-368

VESSEY, M.P. and DOLL, R. (1968). Investigation of relation between use of oral contraceptives and thromboembolic disease. Brit. med. J., 2, 199-205

SPEIZER, F.E. and DOLL, R. (1968). A century of asthma deaths in young people. Brit. med. J., 3, 245-246

DOLL, R. (1968). Hospital records in the computer age. Proc. roy. Soc. Med., 61, 709-715

DOLL, R. (1968). Epidemiology of cancer. Proc. Roy. Soc. Med., 61, 731-732

DOLL, R. (1968). Introductory remarks. A Symposium on Carbenoxolone Sodium (held November 1967). Ed. J.M. Robson and F.M. Sullivan. Butterworth, London, pp.47-49

DOLL, R. (1968). The age distribution of cancer in man. In: Cancer and Aging (Thule Symposium, held September 1967). Ed. Engel and Larsson. Nordiska Bokhandelns Forlag, pp.15-36

AHLUWALIA, H.S. and DOLL, R. (1968). Mortality from cancer of the cervix uteri in British Columbia and other parts of Canada. Brit. J prev. soc. Med., 22, 161-164

DOLL, R. (1968). Carcinogens in the environment: human evidence. T. norske Laegeforen, 88, 1187-1194

DOLL, R. (1968). The geographical distribution of cancer. T. norske Laegeforen, 88, 1160-1165

KNOX, J.F., HOLMES, S., DOLL, R. and HILL, I.D. (1968). Mortality from lung cancer and other causes among workers in an asbestos textile factory. Brit. J. industr. Med., 25, 293-303

RESEARCH COMMITTEE OF BTA (incl. R. DOLL) (1968). Aspergillus in persistent lung cavities after tuberculosis. Tubercle, 49, 1-11

1969 COOK, P., DOLL, R. and FELLINGHAM, S.A. (1969). A mathematical model for the age distribution of cancer in man. Int. J. Cancer, 4, 93-112

BOYD, J.T., DOLL, R., HILL, G.B. and SISSONS, H.P. (1969). Mortality from primary tumours of bone in England and Wales, 1961-63. Brit. J. prev. soc. Med., 23, 12-22

1969 151.*STUKON. M. and DOLL, R. (1969). stric cancer in man
contd and physical activity at work. Int. J. Cancer, 4, 248-254

153.*MRC WORKING PARTY (incl. R. DOLL) (1969). Hypogammaglobulinaemia in the United Kingdom. Lancet, 1, 163-168

154.*DOLL, R. (1969). Recognition of unwanted drug effects. Brit. med. J., 2, 69-76

155. DOLL, R. (1969). The geographical distribution of cancer. Brit. J. Cancer, 23, 1-8

156.*DOLL, R. (1969). Comparisons of cancer incidence: statistical aspects. Cancer in Africa, 14, 1-6

157.*BURNS-COX, C.J., DOLL, R. and BALL, K.P. (1969). Sugar intake and myocardial infarction. Brit. Heart J., 31, 485-490

158.*VESSEY, M.P. and DOLL, R. (1969). Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. Brit. med. J., 2, 651-657

159.*DOLL, R. et al (1969). Summarising statement on results of treatment. UICC Monograph Series Vol. 12, Thyroid Cancer. Ed. C. Hedinger. Springer-Verlag, Berlin, pp.309-312

160.*FLETCHER, C. and DOLL, R. (1969). A survey of doctors' attitudes to smoking. Brit. J. prev. soc. Med., 23, 145-153

160A DOLL, R. (1969). Kezelesek ertekelese (evaluation of treatment). Orvoskepzes, 44, 384-394

161.*DOLL, R. and VESSEY, M.P. (1969). Effects on the vascular system and blood: epidemiological studies. In: Metabolic Effects of Gonadal Hormones and Contraceptive Steroids. Plenum Press, pp.563-579

162. DOLL, R. (1969). Documentazione ospedaliera nell'epoca dei calcolatori elettronici (hospital records in the computer age). Applicazioni bio-mediche del calcolo elettronico, 2, 61-72

1970 163.*DOLL, R. and VESSEY, M.P. (1970). Evaluation of rare adverse effects of systemic contraceptives. Brit. med. Bull. 26, 33-38

164.*BOYD, J.T., DOLL, R., FAULDS, J.S. and LEIPER, J. (1970). Cancer of the lung in iron ore (haematite) miners. Brit. J. industr. Med., 27, 97-105

1970 contd 165.*BENNET A.E., DOLL, R. and HOWEL R.W. (1970). Sugar consumption and cigarette smoking. Lancet, 1, 1011-1014

166.*MRC COMMITTEE ON NITROUS OXIDE & OXYGEN ANALGESIA IN MIDWIFERY (incl. R. DOLL) (1970). Clinical trials of different concentrations of oxygen and nitrous oxide for obstetric analgesia. Brit. med. J., 1, 709-713

167.*VESSEY, M.P., DOLL, R., FAIRBAIRN, A.S. and GLOBER, G. (1970). Postoperative thromboembolism and the use of oral contraceptives. Brit. med. J., 3, 123-126

168.*DOLL, R. (1970). The long-term effects of steroid contraceptives. J. biosoc. Sci., 2, 367-389

RESEARCH COMMITTEE OF BTA (incl. R.DOLL) (1970). Aspergilloma and residual tuberculous cavities - the results of a resurvey. Tubercle, 51, 227-245

169.*DOLL, R. (1970). Practical steps towards the prevention of bronchial carcinoma. Scot. med. J., 15, 433-447

170.*DOLL, R. and KINLEN, L.J. (1970). Immunosurveillance and cancer: epidemiological evidence. Brit. med. J., 4, 420-422

170A DOLL, R., MUIR, C. and WATERHOUSE, J. (eds) (1970). Cancer Incidence in Five Continents, II. Springer-Verlag, Berlin, for UICC

1971 171.*DOLL, R. (1971). Unwanted effects of drugs. Brit. med. Bull., 27, 25-31

172.*DOLL, R., MORGAN, L.G. and SPEIZER, F.E. (1971). Cancers of the lung and nasal sinuses in nickel workers. Brit. J. Cancer, 24, 623-632

173.*FRASER, P. and DOLL, R. (1971). Geographical variations in the epidemic of asthma deaths. Brit. J. prev. soc. Med., 25, 34-36

174.*FRASER, P., SPEIZER, F.E., WATERS, S.D.M., DOLL, R. and MANN, N.M. (1971). The circumstances preceding death from asthma in young people in 1968 to 1969. Brit. J. Dis. Ches 65, 71-84

175.*DOLL, R. and FRASER, P. (1971). An epidemic of asthma deaths and its relation to drug therapy. Proc. XII Mtg. Europ. Soc. Study Drug Toxicity (Uppsala, 1970). Excerpta Medica Internat. Cong. Ser. No. 220, pp.133-137

1971 contd 176. DOLL, (1971). The age distribution of cancer: implications for models of carcinogenesis. J. roy. statist. Soc. Series A., 134, 133-166

177.* GLOBER, G., DOLL, R., FAIRBAIRN, A.S. and VESSEY, M.P. (1971). Peptic ulceration and the use of oral contraceptives Brit. J. prev. soc. Med., 25, 144-146

178.* GLOBER, G.A., CANTRELL, E.C., DOLL, R. and PETO, R. (1971). Interaction between ABO and Rhesus blood groups, the site of origin of gastric cancers, and the age and sex of the patient. Gut, 12, 570-573

179.* VESSEY, M.P., DOLL, R. and SUTTON, P.M. (1971). Investigation of the possible relationship between oral contraceptives and benign and malignant breast disease. Cancer, 28, 1395-1399

1971A DOLL, R. (1971). Cancer and aging: the epidemiologic evidence. Oncology 1970, 5, 1-28. Year Book Medical Publishers, Chicago

1971B DOLL, R. (1971). Cancer following therapeutic external radiation. Oncology 1970, 5, 96-102. Year Book Medical Publishers, Chicago

URL 11731

1972 1972C DOLL, R. (1972). Cancer in five continents. Proc. roy. Soc. Med., 65. 49-55

180.* DOLL, R. and PIKE, M.C. (1972). Trends in mortality among British doctors in relation to their smoking habits. J. roy. Coll. Physcns London, 6, 216-222

1972A DOLL, R. (1972). The Epidemiology of Leukaemia. Leukaemia Research Fund, London

182. DOLL, R. (1972). Der ewert epidemiologischer Melhoden fur die Aufdeckung unerwunschte Arzneimittelwirkungen. Der Internist, 13, 301-309 (translation of article in Brit. med. Bull., 27, 25-31, 1971)

183.* FRASER, P.M., DOLL, R., LANGMAN, M.J.S., MISIEWICZ, J.J. and SHAWDON, H.H. (1972). Clinical trial of a new carbonen-oxolone analogue (BX24), zinc sulphate, and vitamin A in the treatment of gastric ulcer. Gut, 13, 459-463

1972A DOLL, R. (1972). Cancers related to smoking. In: Proceedings of the Second World Conference on Smoking and Health. Ed. R.F. Richardson. Pitman Medical, London, pp.10-23

1972 cont'd

184.* DOLL, [illegible] (1972). Retrospective [illegible]dies. In: AMAPI Symp[illegible]um on Adverse Drug Reactic[illegible]. Ed. D.J. Richards and R.K. Rondel. Churchill Livingstone

185.* VESSEY, M.P., DOLL, R. and SUTTON, P.M. (1972). Oral contraceptives and breast neoplasia - a retrospective study. Brit. med. J., 3, 719-723

186.* VESSEY, M.P., DOLL, R., PETO, R. and REDMAN, C.W.G. (1972). Characteristics of women using different methods of contraception - some preliminary findings from a prospective study. Int. J. Epidem., 1, 119-123

187. DOLL, R., VESSEY, M.P., BEASLEY, R.W.R., BUCKLEY, A.R., FEAR, E.C., FISHER, R.E.W., GAMMON, E.J., GUNN, W., HUGHES, G.O., LEE, K. and NORMAN-SMITH, B. (1972). Mortality of gasworkers - final report of a prospective study. Brit. J. industr. Med., 29, 394-406

1974 VESSEY, M.P. and DOLL, R. (1972). Thymectomy and cancer - a follow-up study. Brit. J. Cancer, 26, 53-58

1973 1978 MRC WORKING PARTY ON THERAPEUTIC TRIALS IN LEUKAEMIA (incl. R. DOLL) (1973). Report on the first myelomatosis trial. Part 1, Analysis of presenting features of prognostic importance. Brit. J. Haematol., 24, 123-139

188. DOLL, R. (1973). Hazards of the first nine months: an epidemiologist's nightmare. J. Irish med. Ass., 66, 117-126

189.* DOLL, R. (1973). Monitoring the National Health Service. Proc. roy. Soc. Med., 66, 729-740 (Nuffield Lecture)

190.* DOLL, R. (1973). Oral contraceptives: a medical audit. Community Health, 5, 32-48 (Harben Lecture, 1972)

191.* DOLL, R. (1973). Osler's English School (Osler Oration, 197 Medical History, 3, 217-222

192.* BOYD, J.T., DOLL, R. and GURD, C.H. (1973). Cancer incidenc in Fiji. Int. J. Epidem., 2, 177-187

193.* KINLEN, L.J. and DOLL, R. (1973). Trends in mortality from cancer of the uterus in Canada and in England and Wales Brit. J. prev. soc. Med., 27, 146

1974 DOLL, R. and VODOPIJA, I. (1973). (Eds). Host Environment Interactions in the Aetiology of Cancer in Man. IARC Scientific Publications No. 7. IARC, Lyon

URL 11732

1973 contd DOLL, R. (1973). Age. In: Host Environment Interactions in the Aetiology of Cancer in Man. Ed. R. Doll and I. Vodopija. IARC Scientific Publications No. 7. IARC, Lyon

1974 *DOLL, R. (1974). The causes and prevention of oesophageal cancer. Annual of the Faculty of Medicine (Aristotelian University of Thessaloniki), Vol.X. (Symeonides Memorial Volume)

*DOLL,R. (1974). The Open Arms. Osler Library Newsletter, No. 15. McGill University, Montreal

*DOLL,R. (1974) Smoking, lung cancer, and Occam's razor. New Scientist, 21 February

DOLL,R. (1974). Oesophageal cancer: a preventible disease? In: Monograph 1, International Seminar on Epidemiology of Oesophageal Cancer. Indian Cancer Society, Bombay

VESSEY,M.P. JOHNSON,B., PETO,R. and DOLL,R. (1974). Outcome of pregnancy in women using an intrauterine device. Lancet, 1, 495-498.

*MRC WORKING PARTY ON THE USE OF ANTI-D IMMUNOGLOBULIN FOR THE PREVENTION OF ISOIMMUNISATION OF Rh-NEGATIVE WOMEN DURING PREGNANCY (incl. R. DOLL) (1974). Controlled trial of various anti-D dosages in suppression of Rh sensitization following pregnancy. Brit. med. J., 2,

*ARMSTRONG,B., STEVENS,N. and DOLL,R. (1974). A retrospective study of the association between use of rawolfia derivatives and breast cancer in English women. Lancet, 2,

URL 11733

DOLL,R. (1974). To measure NHS progress. Fabian occasional paper 8. Fabian Society, London

*DOLL,R. (1974). Surveillance and monitoring. Int. J. Epidem., 3, 305-313

*DOLL,R. (1974). Public benefit and personal privacy: the problems of medical investigation in the community. Proc. roy. Soc. Med., 67, 1281-1286

*ARMSTRONG, B. and DOLL,R. (1973). Bladder cancer mortality in England and Wales in relation to cigarette smoking and saccharin consumption. Brit. J.Prev. soc. Med., 28., 233-240

DOLL,R. (1974). Measuring the progress of a health service. N.Z. med. J., 80, 325

DOLL,R. (1974). Oral contraception: a medical audit. N.Z. med. J., 80, 253-257

1975 204. ARMSTRONG, B. and DOLL, R. (1975) Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int. J. Cancer, 15, 617-631

205. VESSEY, M.P., DOLL, R. and JONES, K. (1975). Oral contraceptives and breast cancer. Progress report of an epidemiological study. Lancet, 1, 941

206.*DOLL, R. (1975). The effect of changes in the environment on the health of the community - an epidemiologist's view. J. roy. Coll. Gen. Pract., 25, 326-334

207. ARMSTRONG, B. and DOLL, R. (1975). Bladder cancer mortality in diabetics in relation to saccharin consumption and smoking habits. Brit. J. prev. soc. Med., 29, 73-81

208.*MANN, J.I., VESSEY, M.P., THOROGOOD, M. and DOLL, R. (1975). Myocardial infarction in young women with special reference to oral contraceptive practice. Brit. med. J., 2, 241-245

209* DOLL, R. (1975). Pott and the prospects for prevention. Brit. J. Cancer, 32, 263-272

210. MRC WORKING PARTY ON LEUKAEMIA IN ADULTS (incl. R. DOLL) (1975). The relation between morphology and other features of acute myeloid leukaemia and their prognostic significance. Brit. J. Haemat., 31, 165-179

211. DOLL, R. (1975). Medical research in the public interest. In: Health Care Teaching and Research. Ed. W.C. Gibson. University of British Columbia Press

211a.* DOLL, R. (1975). Discussion paper. N.Y. Acad. Sci., 246 320-321

212.* DOLL, R. (1975). Pott and the path to prevention. Arch. Geschwulstforsch., 45/6, 521-531

213. DOLL, R. (1975). The epidemiology of cancers of the breast and reproductive system. Scot. med. J., 20, 305

214.* ARMSTRONG, B., GARROD, A. and DOLL, R. (1975). A retrospective study of renal cancer with special reference to coffee and animal protein consumption. Brit. J. Cancer, 33, 127

1976 215.* SMITH, P.G. and DOLL, R. (1976). [illegible] irradiation in patients treated for metropathia haemorrhagica. Brit. J. Radiol., 49, 224-232

216.* DOLL, R. (1976). The contribution of epidemiology to knowledge of cancer. Revue d'epidemiologie et de sante publique, 24, 107-[illegible]

217. ARMSTRONG, B., SKEGG, D., WHITE, G. and DOLL, R. (1976). Rauwolfia derivatives and breast cancer in hypertensive women. Lancet, 2, 8

218. MANN, J.I., DOLL, R., THOROGOOD, M., VESSEY, M.P. and WATERS, W.E. (1976). Risk factors for myocardial infarction in young women. Brit. J. prev. soc. Med., 30, 94-100

219. VESSEY, M.P., DOLL, R., PETO, R., JOHNSON, B. and WIGGINS, P. (1976). A long-term follow-up study of women using different methods of contraception: an interim report. J. biosoc. Sci B, 373-425

220. DOLL, R. (1976). Epidemiology of cancer: current perspectives. Am. J. Epidem., 104, 396-404

221.* VESSEY, M.P. and DOLL, R. (1976). Is "the pill" safe enough to continue using? Proc. roy. Soc. Lond. B, 195, 69-80

222.* DOLL, R. and PETO, R. (1976). Mortality in relation to smoking: 20 years' observations on male British doctors. Brit. med. J., 2, 1525-1536

UAL 11735

1977 223. DOLL, R. and PETO, R. (1977). Mortality among doctors in different occupations. Brit. med. J., 1, 1433-1436

224.* SKEGG, D.C.G., DOLL, R. and PERRY, J. (1977). Use of medicines in general practice. Brit. med. J., 1, 1561-1563

225.* DOLL, R., MATHEWS, J.D. and MORGAN, L.G. (1977). Cancers of the lung and nasal sinuses in nickel workers: a reassessment of the period of risk. Brit. J. prev. soc. Med., 34, 102

226.* SMITH, P.G., DOLL, R. and RADFORD, E.P. (1977). Cancer mortality among patients with ankylosing spondylitis not given X-ray therapy. Brit. J. Radiol., 50, 728-734

227.* DOLL, R. (1977). The prevention of cancer. J. roy. Coll. Phycns., 11, 125

1977 contd 228. DOLL, [illegible] (1977). Strategy for detection of [illegible] to man. Nature, 265, 589-596

229.* RADFORD, E.P., DOLL, R. and SMITH, P.G. (1977). Mortality among patients with ankylosing spondylitis not given X-ray therapy. New Engl. J. Med., 297, 572-576

230.* DOLL, R. (1977). Smoking and disease: prospects for control. Royal Society of Health, August 1977

231.* SKEGG, D.C.G. and DOLL, R. (1977). Frequency of eye complaints and rashes among patients receiving practolol and propranolol. Lancet, 2, 465-478

232.* PETO, J., DOLL, R., HOWARD, S.V., KINLEN, L.J. and LEWINSOHN, H.C. (1977). A mortality study among workers in an English asbestos factory. Brit. J. industr. Med., 34, 169-173

UHL 11736

233. DOLL, R. (1977). General epidemiology. In: Topics in Gastroenterology. 5. Cancer of the Large Bowel. Ed. S.C. Truelove and E. Lee. Blackwell Scientific Publications. Oxford, pp.3-

234.* SKEGG, D.C.G. and DOLL, R. (1977). The case for recording events in clinical trials. Brit. med. J., 2, 1523-1524

235.* DOLL, R. (1977). Introduction. In: Origins of Human Cancer Cold Spring Harbor Laboratory, New York, pp.1-12

236. DOLL, R. and KINLEN, L.J. (1977). Fluoridation of water and cancer mortality in the USA. Lancet, 1, 1300-1302

1978 237. MRC WORKING PARTY ON LEUKAEMIA IN CHILDHOOD (incl. R. DOLL) (1978). Immunotherapy of acute myeloid leukaemia. Brit. J. Cancer, 37, 1-14

238.* DOLL, R. (1978). Atmospheric pollution and lung cancer. Environmental Health Perspectives, 22, 23-31

239* CZDERLOF, R., DOLL, R., FOWLER, B., FRIBERG, L., NELSON, N. and VOUK, V. (1978). Air pollution and cancer: risk assessment methodology and epidemiological evidence. Environmental Health Perspectives, 22, 1-12

240.* SMITH, P.G. and DOLL, R. (1978). Age and time dependent changes in the rates of radiation-induced cancers in patie with ankylosing spondylitis following a single course of X-ray treatment. In: Late Biological Effects of Ionizing Radiation, Vol. I. International Atomic Energy Agency, Vienna, 1978

1977 contd

228. DOLL, R (1977). Strategy for det[illegible]on of cancer hazards to man. Nature, 265, 589-596

229.* RADFORD, E.P., DOLL, R. and SMITH, P.G. (1977). Mortality among patients with ankylosing spondylitis not given X-ray therapy. New Engl. J. Med., 297, 572-576

230.* DOLL, R. (1977). Smoking and disease: prospects for control. Royal Society of Health, August 1977

231.* SKEGG, D.C.G. and DOLL, R. (1977). Frequency of eye complaints and rashes among patients receiving practolol and propranolol. Lancet, 2, 465-478

232.* PETO, J., DOLL, R., HOWARD, S.V., KINLEN, L.J. and LEWINSOHN, H.C. (1977). A mortality study among workers in an English asbestos factory. Brit. J. industr. Med., 34, 169-173

233. DOLL, R. (1977). General epidemiology. In: Topics in Gastroenterology. 5. Cancer of the Large Bowel. Ed. S.C. Truelove and E. Lee. Blackwell Scientific Publications, Oxford, pp.3-

234.* SKEGG, D.C.G. and DOLL, R. (1977). The case for recording events in clinical trials. Brit. med. J., 2, 1523-1524

235.* DOLL, R. (1977). Introduction. In: Origins of Human Cancer. Cold Spring Harbor Laboratory, New York, pp.1-12

236. DOLL, R. and KINLEN, L.J. (1977). Fluoridation of water and cancer mortality in the USA. Lancet, 1, 1300-1302

1978

237. MRC WORKING PARTY ON LEUKAEMIA IN CHILDHOOD (incl. R. DOLL) (1978). Immunotherapy of acute myeloid leukaemia. Brit. J. Cancer, 37, 1-14

238.* DOLL, R. (1978). Atmospheric pollution and lung cancer. Environmental Health Perspectives, 22, 23-31

239* CZDERLOF, R., DOLL, R., FOWLER, B., FRIBERG, L., NELSON, N. and VOUK, V. (1978). Air pollution and cancer: risk assessment methodology and epidemiological evidence. Environmental Health Perspectives, 22, 1-12

240.* SMITH, P.G. and DOLL, R. (1978). Age and time dependent changes in the rates of radiation-induced cancers in patients with ankylosing spondylitis following a single course of X-ray treatment. In: Late Biological Effects of Ionizing Radiation, Vol. I. International Atomic Energy Agency, Vienna, 1978

URL 11737

1978 contd

241 WRIGHT,N.H., VESSEY,M.P., KENWARD,B., McPHERSON,K., and DOI . (1978). Neoplasia and plasia of the cervix ute.. and contraception: a poss..le protective effect of the diaphragm. Brit. J. Cancer, 38, 274-279

242 DOLL,R. (1978). Prevention: some future perspectives. Prev. Med., 7, 486-497

243 DOLL,R. (1978). Geographical variation in cancer incidence: a clue to causation. World J. Surg., 2, 595-602 (Grey Turner Lecture, Kyoto, Japan, 1977)

244 DOLL, R. (1978). An Epidemiological Perspective of the Biology of Cancer. Cancer Research, 38, 3573-3583

245 DOLL,R. and Peto,R. (1978). Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. J. Epidem. & Community Health, 32, 303-313

— MRC WORKING PARTY ON LEUKAEMIA IN CHILDHOOD (1978) (incl. R.DOLL) Effect of varying radiation schedules, cyclophosphamide treatment, and duration of treatment in acute lymphoblastic leukaemia. Brit. Med. J., 2, 787-791

1979

246 VESSEY,M.P., DOLL,R., NORMAN-SMITH,B., and HILL,I.D. (1979). Thymectomy and Cancer: A further report. Br. J. Cancer, 39, 193-195

247 SKEGG,D.C.G., RICHARDS,S.M., and DOLL,R. (1979). Minor tranquillisers and road accidents. BMJ, 1, 917-919

248 VESSEY,M.P., DOLL,R., JONES, KEENA, McPHERSON,K., and YEATES,D. (1979). An epidemiological study of oral contraceptives and breast cancer. BMJ, 1, 1757-1760

URL 11738

249 DOLL,R. (1979). Contraception and cardiovascular accidents. INSERM, 83, 17-30

250 DOLL,R. (1979). The pattern of disease in the post-infection era: national trends. Proc. Roy. Soc., 205, 47-61. (also Preface, Proc. Roy. Soc., 205, 3-4)

251 DOLL,R. (1979). Nutrition and cancer: a Review. Nutrition and Cancer, 1, 35-45

252 DOLL,R. (1979). Epidemiology of cervix cancer. Advances in Medical Oncology, Research and Education, vol. 8, ed. N.Thatcher, Pergamon Press, Oxford.

253 DOLL,R., (1979). Smoking, Industrial Pollutants and their interactions. Advances in Medical Oncology, Research and Evaluation, vol. 11, ed. P.M. Wilkinson pp 9-14. Pergamon Press, Oxford.

254 MEDICAL RESEARCH COUNCIL WORKING PARTY ON LEUKAEMIA IN ADULTS (incl. R.DOLL) (1979) Chemotherapy of acute myeloid leukaemia in adults. Brit. J. Cancer, 39, 69-86

255 DOLL,R. (1979). Epidemiological Enquiry - power and limitations. In: Environmental Carcinogenesis Ed. P. Emmelot and E. Kriek, Elsevier, Amsterdam

256 KINLEN,L.J., SHEIL.A.G.R., PETO,J. and DOLL,R. (1979) Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs. Brit. Med. J., 2, 1461-1466.

257 MEDICAL RESEARCH COUNCIL'S WORKING PARTY FOR LEUKAEMIA IN ADULTS AND THE OXFORD LYMPHOMA GROUP (1979). Light chain isotype associated suppression of normal plasma cell numbers in patients with multiple myeloma. Int. J. Cancer, 24, 385-393

1980 258 DOLL,R., GRAY,R., HAFNER,B., and PETO,R. (1980) Mortality in relation to smoking: 22 years' observation on female British doctors. Brit. Med. J. 280, 967-971

259 DOLL,R. (1980). The epidemiology of cancer. Cancer, 45, 2475-2485.

260 HARRIS,R.W.C., BRINTON,L.A., COWDELL,R.H., SKEGG,D.C.G., VESSEY,M.P., and DOLL,R. (1980). Characteristics of women with dysplasia or carcinoma-in-situ of the cervix uteri. Brit. J. Cancer, 42, 359-369

1981 261 DOLL,R. (1980) The interface between epidemiology and cancer control policy. Cancer, 1, 35-50

262 DOLL,R., (1981). Relevance of epidemiology to policies for prevention of cancer in Nickel Toxicology Ed. G.S. Brown pp 3-8 Academic Press, New York

263 CUCKLE,H., DOLL,R., and MORGAN,L.G. (1981) Mortality studies of men working with soluble nickel compounds in Nickel Toxicology, Ed. G.S. Brown, pp 10-14, Academic Press, New York

264 DOLL,R. (1981). Radiation hazards: 25 years of collaborative research. Brit. J. Radiol., 54, 179-186

265 SMITH,P.G., and DOLL,R. (1981) Mortality from cancer and all causes among British radiologists. Brit. J. Radiol., 54, 187-194

266 DOLL,R., and ARMSTRONG,B. (1981) Environmental factors of certain diseases: [illegible]s in Western Diseases: their emergence and prevention. Ed. V.C. Trowell and D.P. Burkett, pp 93-110, Arnold, London

267 PETO,R., DOLL,R., BUCKLEY,J.D., and SPORN,M.B. (1981) Can dietary beta-carotene materially reduce human cancer rates? Nature, 290, 5803-5810 .

268 WALD,N., DOLL,R., and COPELAND,G. (1981) Trends in tar nicotine, and carbon monoxide yields of U.K. cigarettes manufactured since 1934. Brit. Med. J. 282, 763-765

1981 contd.

269 DOLL, R. (1981) Problems of interpreting the epidemiology of oral contraceptive associated liver tumours in Drug Reactions and the Liver. Eds. Davis, M., Tredger, J.M., and Williams, R. pp. 311-312 Pitman Medical, Bath.

URL 11740

270 VESSEY, M.P., McPHERSON, K., and DOLL, R. (1981) Breast cancer and oral contraceptives: findings in Oxford - Family Planning Association contraceptive study. Brit. Med. J., 282, 2092-2094

271 DOLL, R. and PETO, R. (1981) The causes of cancer. Quantitative estimates of avoidable risks of cancer in the United States today. J. Natl. Cancer. Instg., 66, 1195-1308 and [redacted] published by Oxford University Press.

272 DOLL, R. (1981) Relevance of epidemiology to policies for the prevention of cancer. J. Occup. Med., 23, 601-609

273 COX, J.E., DOLL, R., SCOTT, W.A., and SMITH, S. (1981) Mortality of nickel workers: experience of men working with metallic nickel. Brit. J. Industr. Med., 38, 235-239.

274 COOK-MOZAFFARI, P., BULUSU, L., and DOLL, R. (1981) Fluoridation of water supplies and cancer mortality. I. A search for an effect in the U.K. on risk of death from cancer. J. Epidem. Community Hlth., 35, 227-232.

275 COOK-MOZAFFARI, P., and Doll, R. (1981) II. Mortality trends after fluoridation. J. Epidem. Community Hlth., 35, 233-238.

276 KINLEN, L., and Doll, R. (1981) III. A re-examination of mortality in cities in the U.S.A. J. Epidem. Community Hlth., 35, 239-244.

277 BUCKLEY, J.D., HARRIS, R.W.C., DOLL, R., VESSEY, M.P., and WILLIAMS, P.T. (1981) Case-control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. Lancet, 2, 1010-1012

278 MANNING, K.P., SKEGG, D.C.G., STELL, P.M., and DOLL, R. (1981) Cancer of the larynx and other occupational hazards of mustard gas workers. Clin. Otolaryngol., 6, 165-170.

279 DOLL, R. (1981) The smoking-induced epidemic. Canad. J. Publ. Hlth., 72, 372-381.

280 SKEGG, D.C.G., and DOLL, R. (1981) Record linkage for drug monitoring. J. Epidem. Community Hlth., 35, 25-31.

281 SKEGG, D.C.G., RICHARDS, S., and DOLL, R. (1981) Assessment of the 'E' book as a tool for drug monitoring. J. Epidem. Community Hlth., 35, 32-34.

1982

283 SMITH, P.G., and DOLL, R. (1982) Mortality among patients with ankylosing spondylitis after a single treatment course with x-rays. Brit. Med. J., 284, 449-460.

284 VESSEY, M.P., McPHERSON, K., YEATES, D., and DOLL, R. (1982) Oral contraceptive use and abortion before first term pregnancy in relation to breast cancer risk. Brit. J. Cancer, 45, 327-331.

285 SKEGG, D.C.G., CORWIN, P.A., PAUL, C., and DOLL, R. (1982) Importance of the male factor in cancer of the cervix. Lancet, 2, 581-583.

286 DOLL, R., and PETO, R. (1982) Morbidity versus mortality (letter) J. Nat. Cancer Inst., 69, 549-550.

287 DOLL. R. (1982) Oesophageal carcinoma, epidemiology in Topics in Gastroenterology, 10, Eds. D.P. Jewell and W.S. Selby. Blackwell Scientific Publications, Oxford.

288 DOLL, R. (1982) Green College, Oxford: its contribution to clinical medicine. Brit. Med. J., 285, 1805-1806.

289 DOLL, R. (1982) Clinical trials: retrospect and prospect. Statistics in Med., 1, 337-344.

290 DOLL, R. (1982) Prospects for prevention. Royal College of Physicians, London, reprinted Brit. Med. J. (1983), 286, 445-453 and (abbreviated) in World Health Forum, 4, 219-227.

URL 11741

1983

291 DOLL, R. (1982) Underlying concepts of cancer control in the future. In: Cancer Prevention in Developing Countries. Eds. Aoki, K., Tominaga, S., Hirayama, J., and Hiroto, J. University of Nagoya Press, Nagoya.

292 KINLEN, L., DOLL, R., and PETO, J. (1983) The incidence of tumors in human transplant recipients. Transplantation Proceedings, 15, 1039-1042.

293 VESSEY, M., BARON, J., DOLL, R., McPHERSON, K., and YEATES, D. (1983) Oral contraceptives and breast cancer: final report of an epidemiological study. Brit. J. Cancer, 47, 455-462.

294 DOLL, R. (1983) Cancer control. Symposium on Medical Management of Malignant Disease. Royal College of Physicians of Edinburgh, Edinburgh.

295 CUZICK, J., VELEZ, R., and DOLL, R. (1983) International variations and temporal trends in mortality from multiple myeloma. Int. J. Cancer, 32, 13-19.

1983 cont'd 296 FORMAN, D., DOLL, R., and PETO, R. (1983)
Trends in mortality from carcinoma of the liver and the use of oral contraceptives. Brit. J. Cancer, 48, 349-354.

297 DOLL, R. (1983)
Prospects for the prevention of cancer. Clin. Radiol., 34, 609-623.

298 FRANCESCHI, S., DOLL, R., GALLWEY, J., LA VECCHIA, C., PETO, R. and SPRIGGS, A.I. (1983)
Genital warts and cervical neoplasia: an epidemiological study. Brit. J. Cancer, 48, 621-628.

1984 299 WALD, N., BOREHAM, J., DOLL, R., and BONSALL, J. (1984)
Occupational exposure to hydrazine and subsequent risk of cancer. Brit. J. Industr. Med., 41, 31-34.

300 DOLL, R. (1984)
Smoking and death rates. J. Amer. Med. Ass., 251, 2854-2857.

301 DOLL, R. (1984)
Prevention of cancer: practical prospects. Ann. Acad. Med. (Singapore), 13(2), 194-205.

302 DOLL, R. (1984)
Epidemiological discovery of occupational cancers. Ann. Acad. Med. (Singapore), 13(2) (Suppl), 331-339.

303 DOLL, R. (1984)
Occupational cancer: problems in interpreting human evidence. Ann. Occup. Med., 28, 291-305.

304 PETO, R. and DOLL, R. (1984)
Keynote address: the control of lung cancer.
In: Lung Cancer: Causes and Prevention. Verlag Chemie International Inc.

305 DOLL, R. (1984)
The controlled trial. Postgrad. Med. J., 60, 719-724.

306 DOLL, R. (1984)
Nickel exposure: a human health hazard. IARC Scientific Publication No. 53. ed. F.W. Sunderman. pp.3-21.

307 PETO, J., CUCKLE, H., DOLL, R., HERMON, C. and MORGAN, L.G. (1984)
Respiratory cancer mortality of Welsh nickel refinery workers. IARC Scientific Publication No. 53. ed. F.W. Sunderman. pp.37-46.

1985 308 FORMAN, D., AL-DABBAGH, S., and DOLL, R. (1985)
Nitrates, nitrites and gastric cancer in Great Britain. Nature, 313, 620-625.

1985 cont'd

309 DOLL, R. (1985)
Occupational cancer: a hazard for epidemiologists.
Int. J. Epidemiol., 14, 22-31.

310 DOLL, R. (1985)
Relevance of epidemiology to policies for the prevention of cancer. Human Toxicol., 4, 79-116.

311 DOLL, R. and PETO, J. (1985)
Asbestos: Effects on Health of Exposure to Asbestos.
A Report to the Health and Safety Commission, HMSO, London.

312 GREENBERG, E.R., VESSEY, M.P., MCPHERSON, K., DOLL, R. and YEATES, D. (1985)
Body size and survival in premenopausal breast cancer.
Br. J. Cancer, 51, 691-697.

313 PETO, R. and DOLL, R. (1985)
The control of lung cancer.
New Scientist, 24 January, 1985.

314 PETO, J., DOLL, R., HERMON, C., BINNS, W., CLAYTON, R. and GOFF, T. (1985)
Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory.
Ann. Occup Hyg., 29, 305-355.

315 FORMAN, D., BENNETT, B., STAFFORD, J. and DOLL, R. (1985)
Exposure to vinyl chloride and angiosarcoma of the liver: a report of the register of cases.
Brit. J. industr. Med., 42, 750-753.

316 FORMAN, D., AL-DABBAGH, S. and DOLL, R. (1985)
Nitrate and gastric cancer risks. (letter)
Nature, 317, 675-676.

317 DOLL, R. (1985)
Richesses de la Difference.
Recherche Medicale, Sante, Societe. Colloque organise a l'occasion du XXeme anniversaire de L'Institut Nationale de la Sante et de la Recherche Medicale, 27 & 28 Octobre 1984. INSERM, Paris.

318 DARBY, S.C., DOLL, R. and PIKE, M.C. (1985)
Detection of late effects of ionizing radiations: why deaths of A-bomb survivors are a valuable resource.
Int. J. Epidemiol., 14, 637-638.

1986

319 McCANCE, D., KALACHE, A., ASHDOWN, K., ANDRADE, L., MENEZES, F., SMITH, P. and DOLL, R. (1985)
Human papillomavirus types 16 and 18 in carcinoma of the penis from Brazil.
Int. J. Cancer, 37, 55-59.

1986 cont'd

320 NEUBERGER, J., FORMAN, D., DOLL, R. and WILLIAMS, R. (1986)
Oral contraceptives and hepatocellular carcinoma.
Brit. Med. J., 292, 1355-1357.

321 FORMAN, D., VINCENT, T.J. and DOLL, R. (1986)
Cancer of the liver and the use of oral contraceptives.
Brit. Med. J., 292, 1357-1361.

322 HARRIS, R.W.C., FORMAN, D., DOLL, R., VESSEY, M.P. and WALD, N.J. (1986)
Cancer of the cervix uteri and vitamin A.
Brit. J. Cancer, 53, 653-659.

323 AL-DABBAGH, S., FORMAN, D., BRYSON, D., STRATTON, I. and DOLL, R. (1986)
Mortality of nitrate fertiliser workers.
Brit. J. industr. Med., 43, 507-515.

324 DOLL, R. (1986)
The quantitative significance of asbestos fibres in the ambient air.
In: Advances in Aerobiology, Proceedings of the 3rd International Conference on Aerobiology. Eds. G. Boehm and R.M. Leutschner. Birkhaeuser Verlag, Basel.

325 DOLL, R. (1986)
Implications of epidemiological evidence for future progress.
In: Banbury Report 21: Viral Etiology of Cervical Cancer. Eds. R. Peto and H. zur Hausen. pp.321-326. Cold Spring Harbor Laboratory, 1986.

326 DOLL, R. (1986)
Cancer: a world-wide perspective.
In: Biochemical and Molecular Epidemiology of Cancer. UCLA Symposium on Molecular and Cellular Biology. New Series, vol. 40. Ed. C.C. Harris. pp.111-125. Alan R. Liss, New York.

327 DOLL, R. (1986)
Possibilities for the prevention of cancer. A lecture for the public given on 13 November 1986. The Royal Society, 1986.

328 PETO, J. and DOLL, R. (1986)
Passive smoking.
Br. J. Cancer, 54, 381-383.

329 DOLL, R. (1986)
Cancer: a preventable disease?
Royal Society of Medicine, London.

1986 cont'd

330 DOLL, R. (1986)
Tobacco: an overview of health effects.
In: Tobacco: A Major International Health Hazard. Eds. D. Zaridze and R. Peto. IARC Scientific Publications No. 74. International Agency for Research on Cancer, Lyon.

331 KALDOR, J., PETO, J., EASTON, D., DOLL, R., HERMON, C. and MORGAN, L. (1986)
Models for respiratory cancer in nickel refinery workers.
J. Natl. Cancer Inst., 77, 841-848.

1987

332 DARBY, S.C., DOLL, R., GILL, S.K. and SMITH, P.G. (1987)
Long term mortality after a single treatment course with x-rays in patients treated for ankylosing spondylitis.
Br. J. Cancer, 55, 179-190.

333 DOLL, R. (1987)
Future prospects for population health research.
Transactions of the Menzies Foundation, 13, 227-229.

334 DOLL, R. (1987)
The role of epidemiology in the detection and reduction of cancer risks.
Cancer Risks: Strategies for Elimination. Ed. P. Bannasch. pp.14-23. Springer-Verlag, Berlin.

335 DARBY, S.C. and DOLL, R. (1987)
Fallout, radiation doses near Dounreay, and childhood leukaemia.
Brit. Med. J., 294, 603-607.

336 DOLL, R. (1987)
Environmental chemicals and cancer.
Chemistry in Britain, 23, 847-849.

337 FORMAN, D., COOK-MOZAFFARI, P., DARBY, S., DAVEY G., STRATTON, I., DOLL, R. and PIKE, M. (1987)
Cancer near nuclear installations.
Nature, 329, 499-505.

338 DARBY, S.C. and DOLL, R. (1987)
Childhood leukaemia, fallout and radiation doses near Dounreay.
In: Radiation and Health. Eds. R. Russell Jones and R. Southwood. pp. 221-231. John Wiley & Sons Ltd., 1987.

339 McPHERSON, K., VESSEY, M.P., NEIL, A., DOLL, R., JONES, L. and ROBERTS, M. (1987)
Early oral contraceptive use and breast cancer: results of another case-control study.
Brit J. Cancer, 56, 653-660.

1987 cont'd

340 DOLL, R. (1987)
Medicine and Geography.
In: Geography and its Neighbours. School of Geography, University of Oxford Research Papers. Ed. A.D. Treadgold.

341 DOLL, R. and PETO, J. (1987)
Other asbestos related neoplasms.
In: Asbestos-related Malignancy. Eds. K. Antman and J. Aisner. pp. 81-96. Grune & Stratton, Orlando.

342a DOLL, R. (1987)
Major epidemics of the 20th century: from coronary thrombosis to AIDS.
J. roy. Stat. Soc., Series A, 150, 373-395.

1988

342b DOLL, R. (1988)
Major epidemics of the 20th century: from coronary thrombosis to AIDS.
Social Trends, 18, 13-22.

343a DARBY, S.C., KENDALL, G.M., FELL, T.P., O'HAGAN, J.A., MUIRHEAD, C.K., ENNIS, J.R., BALL, A.M., DENNIS, J.A. and DOLL, R. (1988)
Mortality and cancer incidence in UK participants in UK atmospheric nuclear weapon tests and experimental programmes.
Report R214 National Radiological Protection Board, Chilton.

343b DARBY, S.C., KENDALL, G.M., FELL, T.P., O'HAGAN, J.A., MUIRHEAD, C.K., ENNIS, J.R., BALL, A.M., DENNIS, J.A. and DOLL, R. (1988)
A summary of mortality and incidence of cancer in men from the United Kingdom who participated in the United Kingdom's atmospheric nuclear weapon tests and experimental programmes.
Brit. med. J., 296, 332-338.

344 PETO, R., GRAY, R., COLLINS, R., WHEATLEY, K., HENNEKENS, C., JAMROZIK, K., WARLOW, C., HAFNER, B., THOMSON, E., NORTON, S., GILLILAND, J. and DOLL, R. (1988)
Randomised trial of prophylactic daily aspirin in British male doctors.
Brit. med. J., 296, 313-316.

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Effects of exposure to vinyl chloride

An assessment of the evidence

by Sir Richard Doll, FRS[1]

DOLL R. Effects of exposure to vinyl chloride: An assessment of the evidence. *Scand J Work Environ Health* 14 (1988) 61—78. This paper reviews the possible effects of vinyl chloride on the mortality of occupationally exposed men and the carcinogenic effects that might be observed in the general population as a result of environmental pollution with vinyl chloride. The results of four studies fulfilling the criteria of providing substantial numbers of observations more than 25 years after first exposure and covering a period long enough for more than 10 % of the workers to have been expected to die constitute the basis for the assessment of the occupational hazards. Other studies provide only supplementary information. The data permit two conclusions. First, men occupationally exposed to vinyl chloride have experienced a specific hazard of angiosarcoma of the liver. Second, any other occupational hazards that may have existed have been small. No positive evidence of a hazard of any nonmalignant disease or any type of cancer other than angiosarcoma of the liver has been found except possibly for a small hazard of lung cancer when exposure was heavy. More definite conclusions might be reached if those who have studied exposed employees could present their results in appropriate and comparable ways. A very small risk of angiosarcoma may have occurred as a result of vinyl chloride escaping into the environment around plants handling vinyl chloride in the past, but the evidence indicates that the current risk to the general public (if any) must be negligible.

Key terms: angiosarcoma of the liver, cancer, lung cancer, mortality, polyvinyl chloride, review, vinyl chloride monomer.

For many years the inhalation of large amounts of vinyl chloride has been recognized as potentially hazardous. Concentrations of the order of 10 000 ppm in the air induce unconsciousness and cardiac arrhythmia, while prolonged exposure to concentrations an order of magnitude lower have been liable to cause a specific pathological syndrome. This "vinyl chloride illness" has been characterized by four cardinal signs, namely, enlargement of the liver and spleen with a specific histological appearance, patchy infiltration of the skin resembling scleroderma, bony changes in the tips of the fingers described as acroosteolysis, and peripheral circulatory changes identical with the classical picture of Raynaud's disease. These pathological reactions may occur singly or together and may possibly be accompanied by other less characteristic effects. They can, however, be completely avoided if exposure never exceeds the level of a few hundred parts per million, ie, the level to which exposures were generally reduced in the mid-1960s.

One other serious effect has, however, been observed that may not be avoidable in the same relatively easy way, namely, the production of angiosarcoma of the liver. It must, indeed, be presumed that some risk of developing the disease will persist from exposure to doses that are even lower than the current industrial levels of 5 ppm or less, as vinyl chloride has been shown to act as a mutagen (23), and it cannot be assumed that a threshold exists below which no carcinogenic risk persists. Moreover, the possibility has to be considered that vinyl chloride may cause some cancers other than angiosarcoma of the liver, partly because laboratory studies have shown that it causes other cancers in animal experiments and partly because 'the initial studies demonstrating the production of angiosarcoma of the liver in humans were inadequate in size to exclude a material increase in the risk of cancer in common sites, such as the lung and large bowel. Since no threshold dose can be postulated, it also follows that some cancers may have been produced in the general public by the small amounts that have escaped into the general environment.

Consideration also needs to be given to the possibility that exposure to vinyl chloride over a long period may have noxious effects on humans that cannot be seen easily in animal experiments (by, for example, producing chronic respiratory disease), and, as it is a mutagen, there is also a possibility that it may act as a teratogen and cause congenital malformations in offspring.

In this review I have not examined the possibility that vinyl chloride acts as a teratogen or that it causes mutations in germ cells, as there is too little serious evidence to justify inclusion. Reviews carried out for sections of the industry by Downs et al (unpublished report to the Society of Plastic Industries Inc in 1977)

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and by MacMahon (unpublished report to the Chemical Manufacturers Association in 1977) concluded that the few reports of positive effects could not be substantiated, and no additional evidence was found in a similar later review by Barr (unpublished report to Air Products and Chemicals Inc in 1981), apart from a report that embryos were absorbed and skeletal ossification was produced when pregnant rats were exposed to doses appreciably lower than those that had been used by other workers without any such effects being observed. The report of absorbed embryos (34) could not be evaluated thoroughly, however, as the experiment was inadequately described. I have, therefore, examined only the possible effects on the personal health of men occupationally exposed to vinyl chloride, other than those related to their reproductive capacity, and the carcinogenic effects that might conceivably be observed in the general population as a result of the widespread distribution of vinyl chloride as a pollutant.

Occupational hazards

Many studies of workers exposed to vinyl chloride in the manufacture of vinyl chloride monomer (VCM) and polyvinyl chloride (PVC) have been undertaken since it was first found that vinyl chloride could cause cancer in animals (28, 48) and man (10). These investigations have confirmed that exposure causes a hazard of angiosarcoma of the liver and, in several instances, have shown excess incidence or mortality rates that were conventionally statistically significant for other diseases. Conventional tests of statistical significance are, however, designed to help answer single questions defined beforehand, and several findings that might be expected to occur by chance alone once in (say) 20 times must be expected to occur if dozens of rates are examined in each of several sets of independent data. Scientists have, therefore, been faced with the problem of deciding whether the excess rates that have been observed in individual studies are due to occupational hazards or to the vagaries of chance.

This problem can be solved in part with an examination of the results of a sumation of data from comparable studies, that is, by a comparison of the sums of the numbers of deaths observed and expected in each study. This procedure does not require the assumption that the exposures have been the same in each study any more than the same assumption is required for each individual when the results of each study are considered alone. It does require however that each exposed population has been observed over a period when its members were at risk of developing disease (if a genuine hazard existed) and that in each study the reference population from which the expected numbers of deaths were derived was appropriate (that is, at the same risk of developing disease as the exposed population would have been in the absence of exposure). These requirements do not introduce any new complexity, as both are, of course, also required if correct conclusions are to be drawn from the results of the individual studies when they are examined on their own.

Sources of information

Four studies meet the aforementioned requirements, namely, two large national surveys, one reported by Jones (25) for the United Kingdom (UK) and the other by Environmental Health Associates (14) for the United States (US), and studies of individual plants in Canada, reported by Thériault & Allard (46) and in Italy, reported (as a part of a national study) by Belli et al (4). All four include observations on men more than 25 years after their first exposure, and the expected number of deaths is, in each case, greater than 10 % of the total number of employees, a value indicating a long average period at risk. Earlier observations on UK and US employees (6, 9, 12, 16, 20, 36, 39, 40, 45, 50) have been subsumed in the national surveys and now serve only as sources of hypotheses and of some detailed information not included in the national reports. Studies of German (49), Norwegian (22), Swedish (7), French (41, and unpublished report of Laplanche et al), Japanese (33, 37), and some other Italian (4) workers provide some supplementary information, but, in general, the periods of observation have not been long enough for useful epidemiologic data to be obtained about diseases that are unlikely to occur within 20 years of first exposure, or they report only selected results which are difficult to interpret, as only excess rates tend to have been selected.

Studies of makers of PVC products have not been included, as the workers have had much less exposure to vinyl chloride than those employed in the manufacture of VCM or PVC and any occupational hazard to which they may have been exposed is more likely to have been produced by PVC dust.

US study. The study carried out by Environmental Health Associates (14) on behalf of the US Chemical Manufacturers Association is the largest and most informative investigation thus far undertaken. It covered 10 173 men who had worked in 37 plants owned by 17 companies — 1 214 men in 11 plants that produced only VCM, 6 848 men in 18 plants that produced only PVC, 935 men in three plants that produced both, and 1 176 men in five plants that produced homopolymers and copolymers, with or without VCM or PVC.

Twenty-two of the plants were in the southern part of the country, 14 were in the northeastern or north central parts, and one was in the west.

Men were included if they had been exposed to vinyl chloride for at least a year before 31 December 1972 and had been employed in 1942 or subsequently (the first year depending on the date the plant began making

or using vinyl chloride and the earliest date that personnel records were deemed to be complete, whichever was the later). Individuals who met these criteria were identified from company records by company personnel.

Racial characteristics were known only for 686 men, 97 % of whom were white, and it was presumed, for the purpose of estimating the number of expected deaths, that all 10 173 men were white.

Follow-up data were obtained from plant and Social Security Administration records and (for men who died after 1979) from the National Death Index. Five plants did not collaborate in the extension of Cooper's (9) earlier study, which had been subsumed in the present investigation, and the 955 employees in these plants who were known to be alive on 31 December 1972 were not followed any further. For the rest, follow-up was attempted to death or 31 December 1982, whichever was the earlier. On this basis 92.7 % of the men were successfully traced. Those who were untraced were excluded from the last date of contact, which was usually the date when employment ceased.

Almost half of the men (46 %) were first employed before 1955. A large proportion was, therefore, observed more than 25 years after first exposure (and in many cases for more than 30 years) when diseases with a long latency period might be expected to be seen.

Short-term workers had been excluded from the cohort, and most of the men had continued in employment for many years, two-thirds being employed for 10 years or more and the average duration of employment being 16 years.

Fifteen hundred and thirty-six men were found to have died. In 1 439 cases, the cause of death was obtained from the death certificate, but no cause was obtained for the other 97 persons (6.3 %).

The numbers of deaths expected from each of 38 causes or groups of causes were obtained by multiplying the person-years at risk by the disease-specific national rates for white males, for the corresponding age groups and five-year periods of the study.

This important study is open to three minor criticisms, which are unlikely to have had any material effects on the results. First, the lists of employees were compiled by company personnel from company records without any independent check. Second, the assumption that all the employees were white will have caused the expected deaths to have been very slightly underestimated, as the few black employees are likely to have had higher mortality rates and there is no reason for supposing that the small sample from which the proportion of black employees was estimated was necessarily representative. Third, an element of uncertainty was introduced by the failure to trace as many as 7.3 % of the employees.

Two other criticisms are more important. First, the expected numbers of deaths were calculated on the assumption that the men would have experienced the same mortality rates as the white male population of the whole country at the corresponding dates. The use of national rates is common practice in studies of industrial populations and tends to result in an overestimation of the expected numbers of deaths so that the employees appear to be unusually healthy. This "healthy worker effect" is well known and has been taken into account in my discussion of the results. A more serious objection to the use of national rates is the way mortality varies from one part of the country to another, due to differences in the prevalence of environmental and social factors unrelated to the occupation of interest. It is, therefore, generally preferable to use state (if not county) rates in place of national rates. With 37 plants, however, it might be thought that their geographic distribution would be sufficiently wide to make the use of national rates appropriate. Unfortunately 22 of the plants were located in the south, and a check would have been desirable to see whether their location could have caused any material distortion of the results.

Second, causes were not obtained for 97 of the 1 536 deaths. This deficiency was allowed for in the calculation of the overall mortality by the inclusion of deaths due to unknown causes. It was not allowed for, however, in the calculation of the disease-specific mortality rates and will have caused the standardized mortality ratios to be underestimated by an average of 6.3 %. For the present purpose, therefore, the numbers of deaths attributed to specific diseases have each been multiplied by 1.0674 [100/(1—97/1536)] and rounded off to the nearest integer.

UK study. The study reported by Jones (25 and unpublished) on behalf of the British Health and Safety Executive covered 5 498 men who were employed for at least one year in jobs that involved potential exposure to VCM for at least 25 % of the work week and who were first employed in the period 1940—1974. Details of the men were compiled from the personnel records of nine chemical plants manufacturing or polymerizing vinyl chloride, and the vital status of the men was determined at the end of 1984 from the records of the National Health Service Central Register. Five thousand four hundred and ninety-eight men were traced (98.9 %). Seven hundred and eighty deaths were identified, and copies of the death certificates [coded to the eighth revision of the International Classification of Diseases (ICD) if they occurred before 1979 and to the ninth revision if they occurred later] were sent to the investigators.

Several specific points about the study need to be noted. First, national mortality rates for England and Wales were calculated for five-year age groups over quinquennial periods for 66 causes of death, and these rates were used in the estimation of the numbers of deaths that might have been expected in the cohort by multiplying them by the corresponding numbers of person-years under observation. Some difficulty which could have been related to the causes of death being

coded according to the eighth and ninth revisions of the ICD was, however, experienced in obtaining suitable rates for all causes of death, and rates for a relatively late period had to be used for estimating the numbers of deaths from many diseases that might have been expected to occur in earlier periods. For two categories the earliest available rates were 1960—1964, for one they were 1965—1969, for 24 they were 1970—1974, and for one they were 1975—1979.

Second, an attempt was made to classify men according to whether they had high, intermediate, or low exposure to VCM or PVC dust, and each man's employment history was recorded according to 12 job titles with advice from the plants concerned. The men were then grouped according to whether exposure to VCM was likely to have been high (group A), exposure to PVC dust was likely to have been high with exposure to VCM low (group B), or exposure to VCM and PVC dust was intermediate and intermittent (group C). All other men, who would generally have had low exposure to both VCM and PVC dust, were classed as group D. Within all the groups, exposure to VCM was likely to have been higher *if it* had begun before 1956.

The study makes an important contribution to the knowledge concerning the long-term effects of vinyl chloride. The use of national rates to calculate the expected numbers of deaths may be justified on the grounds that the men were employed in nine plants, which were presumably distributed about the country, but no details of their location are given. In general, mortality rates tend to be higher in the parts of Britain where heavy industry is located than in other parts of the country so that the expected numbers of deaths are more likely to be biased downwards than upwards; but whether this is so or not needs to be shown.

The use of recent rates to calculate expected numbers of deaths from many specific causes of death was presumably necessary if the diseases were to be studied individually and will have done no harm if the incidence and fatality of the diseases in question remained stable. It would have been desirable, however, for the diseases to have been specified so that the reader would know which were liable to be distorted.

The system used to classify the men into four exposure groups is the sort of system that is commonly used if precise measures of exposure are not available. It creates some difficulties in the statistical analysis if men move from one job to another and are classed (as in this instance) as having had high exposure if they have *ever* had a particular type of employment (eg, ever been employed as an autoclave worker). No evidence is provided to show that the person-years at risk before a man entered the category have been subtracted and added to another exposure group before the numbers of expected deaths were calculated. Movement from one job to another was said to have tended to be out of groups A and B into D, but even so it must be presumed that the expected numbers of deaths in the first two exposure categories are likely to have been overestimated.

Canadian study. The Canadian study (46) was limited to employees of a single plant in Shawinigan, Quebec. The plant, which was situated in an industrial complex, was opened in 1943. VCM and PVC were both made until the late 1960s, when the production of VCM ceased, while the production of PVC continued. An attempt was made to trace all the production workers whose names appeared on the unions' lists or the payrolls of the companies in the whole industrial complex, including the vinyl chloride plant, between 1 January 1948 and 31 December 1972, and contact was made with the worker or his next-of-kin in 1 611 out of 1 659 instances (97.1 %). Detailed occupational and smoking histories were obtained by questionnaire, and 156 men who had been employed by the companies for less than five years were excluded. The remaining men were categorized as (i) exposed to VCM if they had worked on the production of VCM or PVC for *at least five years (451 men)*, (ii) unexposed to VCM if they had worked similarly for less than six months (870 men), and (iii) other men (134 in total). The last group was excluded from the study. Follow-up was closed on 31 December 1977. Copies of the death certificates were obtained, and the causes for all who had died (59 exposed and 233 unexposed) were coded according to the eighth revision of the ICD. Information was also sought for histological or cytological confirmation of all the diagnoses for all the exposed men who had died of cancer.

The results were examined in two ways. First, the mortalities of the exposed and unexposed men were compared after standardization for five-year periods of the study and five-year age groups. Second, the mortality of the exposed men was compared with that expected if the men had had the sex- and age-specific mortality rates recorded in Quebec for the year 1971. In both comparisons the causes of death used were those specified on the death certificate, and the additional pathological information was used later only for interpretation of the results.

Most of the exposed men were exposed for more than 10 years (75 %), the average length of exposure was approximately 17 years, and 44 % were observed more than 25 years after first exposure.

Although small, the study makes a useful contribution to the overall results. The histological review of the cancer cases is particularly helpful. It showed that all eight cancers diagnosed as liver cancer (including two specified as hepatoma and one specified as angiosarcoma) were angiosarcomas of the liver, as well as one that had been diagnosed as angiosarcoma of the peritoneum. Two other cases of angiosarcoma of the liver were found to have been certified as hepatic cirrhosis. It is also helpful to have a comparison between

the exposed and "unexposed" employees of the same companies as it shows that the low mortality observed for all nonmalignant diseases could be attributed to a healthy worker effect and was not due to bias in the recording of exposure (relative risk for all nonmalignant causes compared to that of the "unexposed" men 0.95).

One aspect of the study has to be criticized however, ie, the use of provincial rates for one year (1971) to calculate expected mortality spread over a 30-year period (1948 to 1977 inclusive). Deaths will have tended to bunch up towards the end of the period of observation so that the rates for this particular year may have been fairly representative, but it must have caused some distortion of the expected numbers of deaths, the size (and even the direction) of which is impossible to estimate. For most disease groups the distortion is unlikely to have been large.

Italian study. A study of all men employed in the production of vinyl chloride and PVC in nine Italian plants was begun in 1983. All men were included who were employed for at least six months at any time from the start up of the plant to the end of 1981. The study is still incomplete, but results are now available for men in three plants (4). Two plants (in Ferrara and Rosignana) began operation in 1953. Four hundred and thirty-seven men were employed in one plant and 181 in the other. All but three (from the Ferrara plant) were followed to the end of 1984. Expected deaths were estimated by multiplying the person-years at risk by the corresponding national mortality rates for each five-year age group and each five-year period of the study. The total expected deaths in each case amounted to more than 10 % of the employees in the two plants (12.4 and 12.8 %).

Clinical information was sought about the cause of death of all the 55 employees of the Ferrara plant who had died. Revised diagnoses, which were not used for comparison with the expected deaths, revealed four deaths from cancers of the liver in place of one.

The Ravenna plant did not begin operation until 1959. Six hundred and thirty-eight men were employed. All but four were traced to the end of 1983, and 17 were found to have died. No man could have been followed for more than 24 years, and only 25.1 deaths (3.9 % of the work force) were expected. The data for this plant have not, therefore, been used in the principal analyses. It may be noted, however, that one death was attributed to liver cancer when 0.1 was expected.

Other sources. The Norwegian study (22) provided observations on 454 men who had been employed in a plant in Telemark where VCM had been manufactured from 1950 to 1971 and PVC from 1950 to the end of the study period. Every man was included whose name was recorded in the company's personnel register and health department records who had ever been employed from the start of production to the end of 1969 and had worked for at least one year. The men were followed from 1953 to 1979 inclusive. Deaths and cases of cancer were identified from the records of the Central Bureau of Statistics and the national cancer registry. No reference was made to any men being lost to follow-up, but it can be assumed that the number (if not zero) was small, as all citizens have an identity number which is used by both employers and central agencies. Fifty men were found to have died against 59.34 expected if the sex-, age-, and quinquennium-specific national mortality rates had operated. Twenty-one men were found to have developed 23 cancers against 20.16 cancers expected from the comparable national incidence rates, the use of which was justified by the finding that the incidence in the county in which the plant was situated was between 90 and 95 % of the rate of the country as a whole. One man who had been employed in PVC production developed angiosarcoma of the liver. The observed and expected numbers of cases were given for cancers of the lung, colon, and thyroid, for melanomas, and for all cancers, but no expected numbers were given for other types of cancer. It is evident that several other types of cancer must have been in deficit, as there were eight cases in all against 14.93 expected, and it is difficult to know what weight to give the excesses observed for the reported types of cancer, as they seem likely to have been reported specifically because the numbers were in excess of those expected. The authors noted that one further case of melanoma had occurred after the closure of the study and that one "incipient case" was also known to them.

The German study (49) included the following three groups: (i) 7 021 men who had been exposed to VC in the course of their employment in any of the 11 plants in which VC and PVC had been produced in the Federal Republic of Germany, (ii) 4 820 men who had been employed in seven chemical plants without having had any exposure to vinyl chloride, and (iii) 4 007 men employed in two other plants where PVC was processed. Employees were included only if they were of German or Austrian nationality, and they were regarded as exposed to vinyl chloride if they were production workers or other skilled workers or laborers assigned regularly to the plants, but not if they were employed in them only occasionally. All the men were included from the time of opening of the plants to the end of 1974, and they were followed to the end of 1974. Many of the men were therefore observed for only a few years after first employment, and only 14, 36, and 19 %, respectively, of the three groups were first employed before 1954 and were therefore capable of contributing person-years at risk more than 20 years after first employment, when an occupational hazard of cancer could be expected to be observed.

Of the exposed group 93.2 % were successfully followed, and causes of death were discovered for 92.8 % of the 414 men discovered to have died. The proportions for the other two groups were respectively 89.8 and 88.7 % for the unexposed and 92.1 and 86.9 % for the PVC process workers. The failure to obtain causes of death for all the men who had died was allowed for in the subsequent analysis by the weighting of the numbers attributed to each cause by a system which took account of the age group and calendar period in which death with an unknown cause occurred. The expected numbers of deaths from each cause was calculated by multiplying the person-years at risk by the sex-, age-, and cause-specific mortality rates for the Federal Republic of Germany. National data before 1968 used an idiosyncratic classification system, and the 1968 rates had to be used to multiply all the person-years at risk up to the end of 1968. For subsequent years (1969 to 1974) the person-years at risk were multiplied by the corresponding rates for the same calendar year.

Epidemiologic studies are more difficult to carry out in the Federal Republic of Germany than in North America, the United Kingdom, or Scandinavia because the medical cause of death is not recorded publicly, and there is no central system which can be used for checking whether an individual is alive or dead. In these circumstances, the German authors have made valiant efforts to obtain reliable data, and the proportions of men in the exposed groups who were not successfully followed (6.8 %) and the proportions of deaths for which the cause was not obtained (7.2 %) were similar to those in the study of the Environmental Health Associates (14).

Two defects, however, make the data less useful. First, no national mortality rates were available before 1968, and the use of the 1968 rates to estimate the numbers of deaths in and before 1968 will have overestimated the numbers attributable to diseases that were becoming more prevalent or were being diagnosed more often and underestimated those due to diseases that were becoming less prevalent. Second, and more importantly, a large proportion of the men had been first employed less than 10 years before the follow-up ended. Therefore the useful observations on the few men who had been exposed long enough to have had much chance of developing an occupational disease with a long latency period must have been swamped by a mass of other observations that had little to contribute. The expected deaths amounted to only 6.2 % of the exposed men, and there is, therefore, little to be gained, and something to be lost, by including the German data in the overview. It may be noted, however, that 12 deaths were attributed to cancer of the liver among the workers exposed to vinyl chloride against 0.9 expected and that smaller excesses were also observed among the unexposed chemical workers (4 observed against 1.1 expected) and the PVC process workers (3 deaths against 0.8 expected).

Two Swedish plants have produced VCM and PVC, one since 1945 and the other since 1971, and employees of the first plant have been studied by Byren et al (7). All persons who had ever been employed when exposure to VCM could occur were listed from the personnel files of the factory. Twenty-one were excluded because they were foreigners who left the country after a short period of employment. The remaining 750 were followed to October 1974. Expected numbers of deaths were estimated by multiplying the person-years at risk by the corresponding age-specific mortality rates for the whole country, and the expected numbers of cancer cases from 1958 to 1971 inclusive (during which period all cancer cases had been registered nationally) were estimated by multiplying by the national age-specific cancer incidence rates. In both instances, the rates used were those recorded in 1969. Fifty-eight deaths were found, but no figure was given for the expected number. Detailed figures were given only for the numbers of deaths and cases observed and expected for cancer of the lung and for cancers of the liver and pancreas combined and for the numbers of deaths from brain cancer and three categories of cardiovascular disease. Two men known to have angiosarcoma of the liver were certified as having died of liver cancer or pancreatic cancer, and a third man died of angiosarcoma of the liver 17 months after the close of the follow-up.

Two French studies provide the results of a long-term follow-up of men employed in one plant (41) and of a short-term follow-up of men employed in 12 plants (Laplanche et al, unpublished). The first provided observations on 1 311 men exposed to vinyl chloride in the production of VCM and PVC and in selected ancillary operations from the opening of the Tavaux plant in 1953 to the end of 1976 (41). Six other employees were excluded from the study because of lack of occupational histories and 160 men because their vital status at the end of the study period was undetermined. Twenty-five men were found to have died against 48.75 expected from contemporaneous sex- and age-specific national mortality rates (3.7 % of the men at risk). One death was attributed to angiosarcoma of the liver, in a man who had been exposed for more than 15 years. The reported data are so incomplete and cover such a relatively short period from the opening of the plant that they add nothing of epidemiologic value to the results of the other studies, apart from the addition of a further case of angiosarcoma.

The second study provided observations on 1 100 men aged 40 to 55 years who, in 1980, were exposed or had been exposed to vinyl chloride in 12 plants, which constituted "most of the French VCM polymerisation plants" (Laplanche et al, unpublished). Many of the men were, or had been, employed at Tavaux and were presumably survivors of the cohort studied by Pierre et al (41). The men were followed for five years, and their morbidity and mortality were compared with those observed for 1 100 men of the same

ages (± 2 years) who were employed in the same plants but who had never been exposed to VCM. The men in both groups were interviewed personally, and information was obtained about their smoking and drinking habits, which were found to be similar in the two groups. The men in the exposed group had been first exposed for an average of about 14 years and had first been employed in the plant about 18 years previously. Morbidity and mortality data were recorded annually by the plant physician, who successfully traced 98 % of the exposed men and 96 % of the referents. One of the exposed men, but none of those unexposed, developed an angiosarcoma of the liver. Data were not given separately for different periods after first employment, and it is impossible to assess the significance of the finding that six of the exposed men developed lung cancer against two of the referents, which may well reflect a chance occurrence of unusually few cases in the reference group, as the proportion of all lung cancers in that group (2 out of 15) was unusually low. One exposed man developed a cancer of the lymphohematopoietic system against none of the referents, but none of the men in either group were known to have developed melanomas or cancer of the brain or thyroid.

A Japanese study has reported the mortality experience of 4 524 men employed for at least one year before 1965 in 25 Japanese plants which began producing VCM or PVC between 1949 and 1964 inclusive (37). The men were followed to 31 October 1975. Twenty-eight percent of the men were observed more than 20 years after first employment, but none was observed more than 26 years. Only 0.6 % of the men were untraced, and copies of the death certificates were obtained for all the 209 men who had died (4.6 % of the initial cohort). Individuals were classified according to the job in which they had been longest employed at the termination of their follow-up, and data were given separately for the 2 546 men classed as employed in PVC production and 1 978 others (including 900 classed as VCM production workers).

If this study is continued for another 10 years, it should provide useful additional information, but the present data include too few observations on men more than 20 years after first exposure to be of any material use. They confirm the evidence of a hazard of liver cancer with six deaths among the PVC production workers against 2.54 expected from national rates, while only one such death was observed among the other workers against 1.82 expected. One of the six deaths from liver cancer among the PVC production workers was certified as due to angiosarcoma of the liver, and at least one of the other liver cancer deaths was due to the same cause. Lung cancer deaths were not in excess (2 observed in PVC workers against 2.33 expected). No data were given for cancers of the lymphatic and hematopoietic systems, for cancer of the brain or thyroid, or for melanomas. The mortality reported by Masuda (33) for 305 Japanese vinyl chloride workers has presumably been subsumed in Nakamura's (37) later and larger study.

Hazards of cancer

The results of the four most useful studies are listed individually in tables 1 and 2. The overall results for all causes, liver cancer, and three broad groups of conditions are shown in table 3, and those for 10 types, or classes, of cancer are presented in table 4. Data have not been reported for each type of cancer in each study, and the sources of the data are, therefore, specified separately for each type. Additional information obtained from four other less informative studies (4, 7, 22, 49) is given in table 5 for seven types or classes of cancer.

Table 3 shows that, apart from cancer of the liver, the overall mortality is what would be anticipated for an industry without any major hazard of accident or disease. In particular the standardized mortality ratio (SMR) of 84 for diseases other than cancer is typical of the ratios that are commonly observed for groups of employed men. A low SMR of this order reflects the "healthy worker effect," which results from the selection process that inevitably excludes some of the least healthy members of the population from industrial employment. This effect does not, however, normally affect the mortality from cancer beyond that observed in the first few years after the start of employment, and an SMR of 102 for cancers other than cancer of the liver is compatible both with the absence of hazard and with SMR values of 84 for other diseases and 77 for accidents, poisonings, and violence.

Angiosarcoma. Death certificates are an unreliable source of information about the histology of cancers that cause death, but there is no reason to suppose that the excess mortality attributed to liver cancer (or, in the US series, liver and gallbladder cancer) is not entirely accounted for by the known hazard of angiosarcoma. Fifteen of the 37 deaths[2] attributed to cancers of the liver and gallbladder in the US series are known to have been due to angiosarcoma of the liver (14). In the UK series, seven of the 11 deaths attributed to liver cancer, not specified as secondary, were known to be angiosarcomas, and they all occurred in autoclave workers against 0.38 expected liver cancers of all types ($P < 10^{-5}$) (25). In the Canadian series, histological review showed that seven of the eight so-called liver cancers were angiosarcomas (one had been described as an angiosarcoma on the death certificate, two as hepatomas, and five as unspecified liver cancers). One so-called liver cancer death was found to have been due to cancer of the sigmoid colon, while one death attributed to angiosarcoma of the perito-

[2] Increased to 39 in table 1 to take account of the 97 extra deaths from an unknown cause.

Table 1. Observed and expected numbers of deaths from different cancers reported in the four principal studies (4, 14, 25, 46). (O = observed number of deaths, E = expected number of deaths)

Type or class of cancer	United States		United Kingdom		Canada		Italy	
	O[a]	E	O	E	O	E	O	E
Buccal cavity and pharynx	13	11.55	4	3.58	0	0.64	1	0.8
Esophagus	7	8.07	6	14.34	.	.	1	0.6
Stomach	11	16.01	26	23.91	.	.	3	3.0
Large intestine	21	28.79	9	13.94	.	.	0	1.2
Rectum	.	.	11	10.49	.	.	.	.
Liver	.	.	11	1.94	8	0.14	1	0.6
Liver and gallbladder	39	5.77	.	.	.	.	.	.
Pancreas	17	18.40	7	9.88	.	.	0	0.7
Other digestive	.	.	.	.	6	5.26	.	.
Larynx	.	.	4	2.21	.	.	1	0.9
Lung	116	115.87	61	82.12	2	5.78	12	6.1
Other respiratory	5	6.38	.	.	.	.	.	.
Bone	2	1.81	.	.	.	.	.	.
Skin (nonmelanoma	6	7.36	.	.	.	.	.	.
Melanoma	.	.	2	1.74	.	.	0	0.2
Prostate	16	15.20	12	9.59	.	.	1	0.7
Testis	.	.	2	1.38	.	.	.	.
Bladder	6	8.46	14	8.00	1	1.33	1	0.7
Kidney	12	9.06	3	4.10			.	.
Other and unspecified urinary	.	.	3	4.29	.	.	.	.
Brain	25	12.76	4	6.18	0	0.60	.	.
Eye and central nervous system	.	.	.	.	.	.	.	.
Thyroid	.	.	2	0.43	.	.	.	.
Lympho- and reticulosarcoma	12	7.98	4	2.35	.	.	.	.
Hodgkin's disease	3	5.45	3	2.50	.	.	0	0.4
Leukemia	14	13.94	7	6.16	1	1.87	0	0.7
Multiple myeloma	11	8.37	2	2.35	.	.	.	.
Other lymphatic								
Other	46	40.50	18	8.12	2	0.95	9	4.5
All cancers	383	341.73	235	228.60	20	16.37	30	21.1

[a] Observed deaths multiplied by 1.0674 and rounded off to the nearest integer to allow for deaths without discovered cause.

Table 2. Numbers of deaths from nonmalignant and all causes reported in the four principal studies (4, 14, 25, 46). (O = observed number of deaths, E = expected number of deaths)

Cause of death	United States		United Kingdom		Canada		Italy	
	O[a]	E	O	E	O	E	O	E
Benign and other unspecified tumors	4	5.08	.	.	.	.	0	0.5
Cerebrovascular disease	75	91.93	.	.	.	.	.	.
Ischemic heart disease	521	597.73	276	288	25	31.67	19	27.4
Other circulatory disease	157	123.55	105	141				
Bronchitis[b]	44	22.83	36	44	6	3.21	3	5.0
Pneumonia	16	31.94	40	61				
Other respiratory disease	15	32.84						
Cirrhosis of the liver	37	56.06	5	5	4[c]	3.85	4	5.2
Other digestive disease	27	39.52	.	.			3	2.7
Disease of the genitourinary system	11	20.41	.	.	.	.	.	.
Other diseases	67	115.68	43	76	2[d]	5.40	2	7.0
Suicide	49	52.78	40	50	2	10.58	1	0.9
Accidents and other violence	130	173.19					4	7.7
All nonmalignant causes	1 153	1 363.54	545	665	39	54.75	36	56.4
All causes	1 536	1 705.27	780	894	59	71.07	66	77.5

[a] See footnote to table 1.
[b] Emphysema in data from the United States.
[c] Includes two cases certified as cirrhosis of the liver which proved to be angiosarcoma of the liver.
[d] Includes one case with cause unknown.

neum was found to have been due to angiosarcoma of the liver (46). In the Italian study, further evidence revealed that three further deaths should have been attributed to cancer of the liver (for a total of four), but only one of the four was described as an angiosarcoma (4).

Table 3. Mortality from cancer of the liver and other causes among vinyl chloride workers in 49 plants in the four principal studies combined (4, 14, 25, 46). (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio)

Cause of death	O	E	SMR
Cancer of the liver[a]	59	8.45	698
Cancer of other sites	609	599.35	102
Other diseases	1 547	1 844.89	84
Accidents, poisonings, and violence	226	295.15	77
All causes	2 441	2 747.84	89

[a] Including cancers of the gallbladder in the series from the United States.

Table 4. Mortality from various cancers among vinyl chloride workers in 49 plants in the four principal studies combined. (O = observed number of deaths, E = exposed number of deaths, SMR = standardized mortality ratio)

Type or class of cancer	O	E	SMR	Source of information[a]
Mouth and pharynx	18	18.57	109	1, 2, 3, 4
Digestive system (other than liver)	125	154.59	81	1, 2, 3, 4
Respiratory system	223	229.36	97	1, 2, 3, 4
Lung	211	214.09	99	1, 2, 4
Genitourinary system	70	62.81	111	1, 2, 3, 4
Melanoma	2	1.94	.	2, 4
Brain	29	19.54	148	1, 2, 3
Thyroid	2	0.43	.	2
Lymphatic and hematopoietic system	57	50.87	112	1, 2, 3, 4
Other	83	63.24	131	1, 2, 3, 4
All other than of the liver	609	599.35	102	1, 2, 3, 4

[a] 1 = United States study (14), 2 = United Kingdom study (25), 3 = Canadian study (46), and 4 = Italian study (4)

Table 5. Mortality[a] from various cancers among vinyl chloride workers: Supplementary evidence (4, 7, 22, 49). (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio)

Type or class of cancer	Federal Republic of Germany (11 plants)		Norway (1 plant)		Sweden (1 plant)		Italy (1 plant)		Four countries combined (14 plants)		
	O	E	O	E	O	E	O	E	O	E	SMR
Digestive system (excluding the liver)	35.0	31.8	3[b]	1.44[b]	.	.	1	1.2	39.0	34.44	113
Lung	23.5	24.6	5	2.84	3	1.78	0	1.5	31.5	30.72	103
Melanoma	.	.	4	0.79	.	.	0	0.1	4.0	0.89	.
Brain	2.1	1.3	.	.	2	0.33	.	.	4.1	1.63	.
Thyroid	.	.	2	0.16	.	.	.	.	2.0	0.16	.
Lymphatic and hematopoietic system	16.5	7.7	.	.	.	.	0	0.7	16.5	8.4	196
Other (excluding the liver)	10.7	24.3	8	14.93	.	.	4	2.0	22.7	41.43	55
All excluding the liver	87.8	89.7	22	20.16	5[c]	2.11[c]	5	5.7	119.8	117.67	102

[a] Incidence and cases in the Norwegian study.
[b] Cancer of the intestine only.
[c] Cancer of the lung and brain only.

Further evidence that the excess mortality from liver cancer (or liver and gallbladder cancer in the US series) can be attributed principally if not wholly to the known hazard of angiosarcoma is obtained in a comparison of the excess deaths with the numbers of deaths from angiosarcomas recorded in the Register of Liver Angiosarcoma Cases (maintained on behalf of the Association of Plastics Manufacturers in Europe by the Imperial Chemical Industry PLC) before the end of the follow-up period (Bennett, unpublished). Fifty-one excess liver cancers are recorded in the combined data, and 49 angiosarcoma are recorded in the Register for

Table 6. Mortality from lung cancer in the series from the United States (US) (14) and the United Kingdom (UK) (25) by characteristics relevant to an occupational hazard. (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio)

Data characteristic[a]	Category 1			Category 2		
	O[b]	E	SMR	O[b]	E	SMR
Observed 20 years or more after first employment (1), others (2)	114	113.66	100	85	93.83	91
Employed 10 years or more in the US (1), others in the US (2)	86	82.45	105	83	83.44	99
Employed before 1956 in the UK (1), others in the UK (2)	62	61.39	101	29	40.50	72
Ever employed as autoclave worker in the UK (1), others in the UK (2)	16	17.06	94	85	74.82	87

[a] The numbers in parentheses designate the category.
[b] See footnote to table 1 for observed deaths in the US.

the relevant periods for the three countries and the two Italian plants[3] that are covered by the survey.

None of the 120 cases yet recorded in the Register were in men who were *first* exposed after 1969, and none of the 45 men affected in North America were first exposed after 1964. All may, therefore, have been exposed to concentrations of several hundred parts per million, and many may have been exposed to concentrations appreciably higher (unpublished report by Barr to Air Products and Chemicals Inc in 1981).

Lung cancer. The idea that exposure to vinyl chloride might cause cancer of the lung was suggested by Monson et al in 1974 (36), when they noted 13 cases against an expected number of 7.9 in a study of proportional mortality. The combined data shown in table 4 do not provide any support for the hypothesis, either for respiratory cancer as a whole (SMR 97) or for the specified data for lung cancer in the US, the UK, and Italy (SMR 99). There are, however, consistently higher risks in the subgroups of men in the US and UK series, in which occupational hazards would be more likely to be seen than in other groups. This circumstance is illustrated by table 6, which shows that the SMR values are slightly higher for men observed 20 years or more after first exposure than for men observed earlier, for men employed before 1956 in the UK than for men first employed after 1955 (when exposure levels are believed to have been lower), for men employed for longer than for shorter periods in the US, and for autoclave workers in the UK (among whom the angiosarcoma cases have mostly occurred) than for other workers. The differences are all small or very small. They are, however, all in the same direction, and the probability that the rates should all be higher in the groups in which an occupational hazard is more likely to be seen in each of the four pairs of groups is 1 in 16.

Additional information from other sources is given in table 5. A total of 30 deaths (or cases) was observed, and this figure increases to 31.5 when allowance is made for the number of deaths due to unidentified causes in the German study (SMR becoming 103). In the German study the SMR was higher for the men who had been exposed for 10 years or more than for those who had been exposed for shorter periods (111 against 79), and, in the Norwegian study, four of the five cases observed occurred in men whose occupations were regarded as involving high exposure against 1.82 of the 2.84 expected. Both the German and the Swedish studies derived the expected numbers of deaths from national mortality rates for a single year towards the end of the study period. The expected numbers of deaths are likely, therefore, to have been overestimated and the SMR values correspondingly underestimated as the mortality from lung cancer had been rising throughout the period of observation.

Brain cancer. The idea that vinyl chloride might cause brain cancer was also suggested by Monson et al (36) when they reported five cases against 1.2 expected. The combined data that are shown in table 4 provide some support for this hypothesis. The cases of Monson et al (36) were, however, observed in US workers and must be presumed to be included in the total reported by Environmental Health Associates (14); therefore they will have contributed a substantial proportion of the total in table 4. As a test of the hypothesis the data of Monson et al ought, therefore, to be subtracted from those in the table. Their investigation was not a cohort study, and their expected deaths do not correspond exactly to those in table 4. If, however, the observed and the expected cases are both subtracted from the totals, twenty-four observed deaths remain against approximately 18.3 expected, a difference which might easily occur by chance (P one-tailed = 0.1).[4]

[3] Twenty-nine were registered as occurring in the United States against an excess of 33; only 20, however, were identifiable in both series. Inquiry has, as yet, failed to reveal information about the histology of the remaining 13 in the cohort study and the origin of the nine extra deaths in the register. Nine deaths were registered as occurring in the United Kingdom against an excess of nine, but one of the registered cases was certified as due to a benign hemangioma and not related to the liver (code 227 in the eighth revision of the International Classification of Diseases). Ten cases were registered as occurring in Canada against an excess of eight; two were recorded as being in men who had been employed for five years, and it is possible that the actual duration had been slightly less than five years with consequent exclusion from the Canadian cohort. One case was registered as occurring in one of the two Italian plants against an excess of less than one.

[4] If the study of Waxweiler et al (50) is regarded as the origin of the hypothesis, 26 deaths are left against 18.94 expected (P one-tailed = 0.07).

Additional information from two other sources is given in table 5. The small excess reported provides little further evidence of an occupational hazard, as one of the two deaths observed in the Swedish study occurred in a young man who had been employed for less than a year when the diagnosis was made, while the excess death rate for brain cancer observed in the German study was less than that observed among chemical workers not exposed to vinyl chloride (2.9 deaths after allowance for deaths from unknown causes against 1.6 expected) and among workers in the PVC fabrication industry (5.9 deaths after allowance for deaths from unknown causes against 1.1 expected).

Cancers of lymphatic and hematopoietic tissues. The idea that vinyl chloride might cause cancer of the lymphatic and hematopoietic tissues — more specifically the lymphatic tissue — was suggested by Tabershaw & Gaffey (45) and by Waxweiler et al (50) in two cohort studies, when they found, respectively, five deaths from lymphomas in the most heavily exposed workers against 2.54 expected and four deaths from cancers of the lymphatic and hematopoietic tissues against 2.5 expected. These small excesses might have been ignored if the laboratory findings had not been interpreted as suggesting that lymphomas were produced experimentally in animals exposed to vinyl chloride by inhalation (29). The idea that similar exposure might also cause lymphomas in humans, therefore, merits serious consideration. The data from the four principal studies that are summarized in table 4 provide little support for the hypothesis when all cancers of the lymphatic and hematopoietic tissues are considered together (57 deaths against 50.87 expected, SMR 112) and very little more is obtained from the separate data for cancers of the lymphatic system (Tabershaw & Gaffey's definition of ICD list numbers, eighth revision, 200—203 and 205 being used) that are shown in table 1 (35 deaths against 29.40 expected). The position is, moreover, hardly altered if the data in Tabershaw & Gaffey's initial report are subtracted (29 deaths against 23.36 expected, SMR 124).

Little additional information is provided by the results of the German study (49). (See table 5.) This study obtained an SMR of 214 for exposed workers (based on 15 observed deaths, increased to 16.5 when allowance is made for the number of deaths from unknown causes) against SMR values of 77 and 34 for an unexposed group of chemical workers and a group of PVC fabricators. It showed that the excess of the exposed workers was present only for men who had been exposed for more than one year and that this excess was most marked for men who had been exposed for five years or more (10.7 deaths after allowance for the number of deaths from unknown causes against 4.0 expected, SMR 268, P one-tailed <0.01).

Melanoma. An excess of melanoma was reported for Norwegian workers by Heldaas et al (22), who raised the possibility that vinyl chloride might have produced the disease. Four cases were observed when 0.79 were expected, and three of the four were in men whose occupations involved the highest exposures (against 0.51 expected). At the time of the writing of their report, one further case had been detected with onset three years after the closure of the study. Subsequent studies in other countries have, so far, reported only two deaths against 2.0 expected. (See tables 1 and 5.)

Thyroid cancer. An excess of thyroid cancer was also reported in the Norwegian study (22), in which two cases were observed against 0.16 expected. The investigators were not aware of any other studies indicating an excess of this type of cancer, and they drew no conclusion from their observation. Two of the three major studies that have been reported since the Norwegian observation was made gave no data for thyroid cancer; the third reported two deaths against 0.43 expected. (See table 1.) One death from thyroid cancer, it may be noted, was reported in the US by Monson et al (36).

Cancers of the digestive tract. Suggestions that vinyl chloride might cause cancers of the digestive tract in general have sometimes been made, but they have not taken adequate account of the contribution of cancers of the liver to the total number of cancers of the digestive system, particularly when it is borne in mind that some liver cancers are likely to be misdiagnosed as cancers of other organs. The combined data from the four principal studies shown in table 4 weigh heavily against the idea that any such effect has been produced.

Other cancers. One of the remaining types, or classes, of cancer listed in table 4 shows a statistically significant excess, namely, the heterogeneous group of "other cancers" (83 observed deaths against 65.24 expected, P two-sided <0.05). This excess is only marginally significant and may be a chance observation. The most likely explanation is, however, that a few angiosarcomas of the liver were not recognized and were diagnosed as secondary liver cancer or carcinomatosis, site unknown, the number of deaths in this category therefore being increased.

Hazards of nonmalignant disease

No previous study has suggested that any nonmalignant cause of death other than cirrhosis of the liver would be likely to be increased as a result of exposure to vinyl chloride, and cirrhosis of the liver is presumed to be increased only because of the liver changes that were observed as part of the "vinyl chloride illness" (24, 31, 33). Two other possibilities have, however, been raised, namely, the production of nonmalignant respiratory disease, because of the changes in lung function and radiographic appearances that have been

Table 7. Mortality from selected nonmalignant causes and all causes in the four principal studies combined. (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio)

Type of disease	O	E	SMR	Source of information[a]
Bronchitis, emphysema[b]	80	66.83	120	1, 2
Other respiratory disease	71	125.78	56	1, 2
All respiratory disease	160	200.82	80	1, 2, 3, 4
Ischemic heart disease	797	885.73	90	1,2
Other circulatory disease[c]	352	384.56	96	1,2
All circulatory disease[c]	1 103	1 209.35	91	1, 2, 3, 4
Cirrhosis of the liver	46	66.26	69	1, 2, 4
Other disease	238	368.07	65	1, 2, 3, 4
All nonmalignant disease	1 547	1 844.50	84	1, 2, 3, 4
All external causes	226	295.15	77	1, 2, 3, 4
All nonmalignant causes	1 773	2 139.65	85	1, 2, 3, 4
All causes	2 441	2 747.85	89	1, 2, 3, 4

[a] 1 = United States study (14), 2 = United Kingdom study (25), 3 = Canadian study (46), and 4 = Italian study (4).
[b] Bronchitis in the United Kingdom study, emphysema in the United States study.
[c] Includes cerebrovascular disease in the United Kingdom and Italian studies.

Table 8. Mortality from chronic obstructive lung disease[a] in the series from the United States (US) (14) and the United Kingdom (UK) (25) by characteristics relevant to an occupational hazard. (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio)

Data characteristic[b]	Category 1			Category 2		
	O	E	SMR	O	E	SMR
Observed 20 years or more after first employment in the US (1), others in the US (2)	30	15.8	190	11	7.0	157
Employed 10 years or more in the US (1), others in the US (2)	16	10.9	147	25	12.0	208
Employed before 1956 in the UK (1), others in the UK (2)	26	30.17	86	10	13.60	74
Ever employed as an autoclave worker in the UK (1), others in the UK (2)[c]	3	6.56	46	33	37.22	89

[a] Described as emphysema in the US study and as bronchitis in the United Kingdom study.
[b] The numbers in parentheses designate the category.
[c] Men ever employed as a bagger or drier, occupations which would have caused the greatest occupational exposure to polyvinyl chloride dust, experienced one death from bronchitis against 4.96 expected.

recorded for men exposed to PVC dust (2, 26, 27, 44), and acute cardiac death, from analogy with the effect of other halogenated hydrocarbons (25) and the observation of an increased mortality from myocardial infarction in the few years following the cessation of exposure in the Swedish PVC processing industry (35). Relevant figures for the numbers of deaths from these and other nonmalignant causes that are obtainable from the four principal studies were given in table 2, and they have been summarized in table 7.

Cirrhosis of the liver. Three of the four principal studies gave separate figures for cirrhosis of the liver, none of which showed an increased mortality (table 2); in combination they gave an SMR of 69 based on 46 deaths. The fourth study, which did not give separate data for cirrhosis of the liver, reported four deaths from all diseases of the digestive system combined against 3.85 expected and noted that the four included two that were certified as due to cirrhosis of the liver, but actually due to angiosarcoma (46). In the two supplementary studies in which data were given for this disease, the SMR was 82 in one, based on 15.1 deaths after allowance for the number with unknown causes (49), and 133 in the other, based on seven deaths (37).

Nonmalignant respiratory disease. The data for nonmalignant respiratory disease are confusing in that the total SMR from the combined data for the four principal studies is 80 and is the sort of figure that is commonly found in healthy industrial populations, yet the US study recorded a substantially increased mortality from emphysema (41 deaths and an SMR of 180 before any allowance was made for deaths from unknown causes). No such excess was found in the UK, where 36 deaths from bronchitis gave an SMR of 82. International comparisons of chronic nonmalignant respiratory disease are complicated by the usage of different terms to describe what it is now agreed is best called chronic obstructive lung (or pulmonary) disease, but which in the past tended to be called emphysema in the US and chronic bronchitis in the United Kingdom. It must, therefore, be presumed that the two categories of "emphysema" and "bronchitis" used respectively in the two large national studies were meant to describe the same thing. One must assume, therefore, that the experiences in the two countries were very different, despite the fact that both related to cohorts that had very similar experiences of angiosarcoma of the liver and so, presumably, fairly similar exposures to vinyl chloride.

Separate figures are shown in table 8, where available, for the mortality observed among men with different durations and intensities of exposure. Unlike the data for cancer of the lung that were shown in table 6, they provide no consistent evidence of a greater risk in the groups in which an occupational hazard would

be expected to be concentrated. The authors of the Environmental Health Associates report (14) were unable to give any explanation for the increased mortality from emphysema, and they point out that it could hardly be due to excess cigarette smoking, as there was no overall excess for cancer of the lung. It is striking, however, that the excess is more than compensated for by deficiencies in the other categories of nonmalignant respiratory disease (pneumonia 15 deaths,[5] SMR 47.0; other respiratory disease 14 deaths, SMR 42.6), and the question arises whether the emphysema excess could be a classificatory artifact. Environmental Health Associates (14) list all the 41 deaths which show that they were coded under ICD number 527 which, in the out-of-date seventh revision that was used for the coding of all deaths in the study, was the code for "other respiratory disease not otherwise classified" and included emphysema. Under that revision, however, emphysema that was associated with bronchitis should be classified with bronchitis under ICD numbers 500 to 502, and the possibility may be considered that some of the emphysema deaths should have been classified in some category of respiratory disease other than ICD number 527. If this were the situation, it could account for both the excess mortality from emphysema and the grossly deficient mortality from other nonmalignant respiratory diseases.

No excess mortality from "bronchitis, emphysema, and asthma" was observed in the German study (SMR 44 with 6.3 deaths observed after allowance for the number of deaths from an unknown cause) (49).

Cardiovascular disease. Data for ischemic (or arteriosclerotic) heart disease (which may be presumed to include the vast majority of all deaths certified as due to acute cardiac disease) were given only by the two big national studies, and they provide no evidence of an increased mortality. The SMR values of 90 for this group of diseases and of 91 for all cardiovascular disease recorded in the four principal studies are typical of the SMR values of healthy industrial populations, and there is no suggestion of any occupational hazard in the subsidiary analyses provided by the two national studies. In particular, there is no evidence of an increased mortality within one month of leaving employment in the UK study either for all workers (52 deaths, SMR 61) or for the most heavily exposed autoclave workers (9 deaths, SMR 42).

A slight increase in ischemic heart disease mortality was recorded for the exposed workers in the German study (49), but it was less than that recorded for the unexposed chemical workers and the PVC fabricators (SMR values of 127, 131, and 158 based on 97.2, 126.7, and 109.7 deaths, respectively, after allowance for the number of deaths from unknown causes).

Discussion

The information that has now been obtained about the long-term health of men occupationally exposed to vinyl chloride is massive and compares favorably with that available for any other occupational group. Two facts are outstanding. First, the men have experienced a specific hazard of a type of cancer that is normally extremely rare, namely, angiosarcoma of the liver. The rarity of this disease under other conditions made the detection of the hazard easy; but the long latency period before the disease appears after first exposure (almost always more than 10 years and usually more than 15 years) meant that a large number of men had been exposed before the hazard was detected and that it will still be many years before the extent of the protection provided by the reduction in exposure in the 1960s and that of the further reduction that followed the recognition of the hazard in 1974 are known. There is, unfortunately, no effective treatment for the disease, and the number of cases is reflected in the number of deaths. Some 50 deaths have occurred among the 16 740 men who were followed in the four principal studies that have been reviewed in this report, so that approximately 1 in 335 men have been affected, 2 % of the deaths having been due to this one cause. Eventually many more men must be expected to develop the disease. One estimate (38) suggests that the total may be increased 10 times, but a more realistic estimate is two to three times (19).

The second outstanding observation is that the mortality of the exposed men, other than that due to angiosarcoma of the liver, is typical of the normally healthy industrial worker — that is not to say that no other hazard exists, but that the effect of any other hazard is small.

The massive data that are now available provide no reason for thinking that any hazard other than one of cancer has been overlooked. It is, however, still difficult to decide whether vinyl chloride produces a risk of developing cancer other than angiosarcoma of the liver which might be small compared to the risks produced by nonoccupational causes, but yet absolutely almost as large as the risk of developing the normally very rare angiosarcoma.

One of the many hazards suggested can be dismissed, as there is no evidence to support it, namely, that of vinyl chloride as a cause of any cancer of the digestive tract other than angiosarcoma of the liver. Two hazards (of melanoma and cancer of the thyroid) have been suggested only very recently, and few of the available studies have provided information about them. There is no good theoretical reason or laboratory evidence to suggest that either should be produced by

[5] The deaths attributed to different groups of respiratory diseases and the corresponding SMR values that are cited in this section for the US study are as given by the Environmental Health Associates (14) and have not been adjusted to account for the number of deaths from an unknown cause. To take account of these deaths, the observed deaths and SMR values can both be multiplied by 1.0674.

vinyl chloride, and, in light of present evidence, the simplest explanation is that the reported excesses are the chance effects that must be expected when many different types of cancer are studied in several different populations. So far as melanoma is concerned, it has to be remembered that the disease has become much more common in recent years in Scandinavia (where the excess was reported) due, it is believed, to the popularity of sunbathing and the increased opportunities for Scandinavians to travel to the warmer parts of Southern Europe and North Africa. The extent to which this change may have affected the observation in Norway needs to be examined.

Two other hazards (of lymphoma and brain cancer) were suggested by the early results of some of the US studies. That vinyl chloride might produce a hazard of lymphoma was initially supported by the preliminary results of animal studies, but the complete results of the many investigations that have been undertaken (see reference 29) do not suggest that lymphoma or any other cancer of the hematopoietic system is liable to be produced. There is, however, some evidence that brain tumors can be produced in rats (29). The hypotheses that lymphomas and brain cancers might be produced by vinyl chloride have been supported by the observation that both these types of cancer have caused death more often than might be expected from national mortality rates, but the excesses observed in the combined data from the four principal studies in this review are small and not statistically significant, and the hypotheses remain unproved. The small excess of brain cancer is particularly difficult to evaluate, as mortality rates from this disease have changed rapidly over time as methods of diagnosis have improved and the suspicion of an occupational hazard (which was raised in 1975) could have influenced the findings. What excess has occurred has been limited to the US and Germany, and the German findings carry little weight, as the excess was found in each of the three occupational groups studied, irrespective of the chemicals to which they were exposed. The supplementary data from the German study showing an increased mortality from lymphatic and hematopoietic cancers are more impressive, particularly as the excess was the most marked for men who had been employed for at least five years. In these circumstances, judgment must still be suspended until the data for each study are analyzed for each specific type of cancer, by intensity and duration of exposure, and by time since exposure began.

There remains the suggestion that vinyl chloride might cause lung cancer. At first sight, this possibility is ruled out by the SMR of 97 for the combined data for respiratory cancer for the four principal studies. Lung cancer is, however, normally so common (accounting for about 8 % of the expected deaths) that an increase in mortality that was half as important (numerically) as the increase in mortality from angiosarcoma of the liver might easily be overlooked (95 % confidence limits of the SMR 85—112). The incidence of the disease varies moreover within a country, and there must be doubts as to whether the national experience provides a suitable reference for men employed in plants that are not evenly distributed about the country. In these circumstances one cannot exclude an occupational hazard unless it can be shown that the mortality of the exposed men is independent of the factors that might be expected to influence it if some of it were occupational in origin, namely, the intensity and duration of exposure and the time since exposure began. It is not possible to examine these relationships in detail, as the reports do not provide all the necessary information. Such information as they do provide, which was summarized in table 6, supports the idea that exposure to vinyl chloride involves a small hazard of lung cancer. Taken in conjunction with the knowledge that lung tumors have been produced in several species of animals exposed to vinyl chloride by inhalation (29), it would seem that a small hazard of lung cancer probably did occur. The evidence is not, however, strong enough to conclude that it definitely did. If it did, the hazard was evident only for men who had been employed for many years at a time when exposures of several hundred parts per million or more were common, and any persisting risk can be only minute and incapable of detection.

The questions that have been left unanswered by this discussion might well be answered definitely if (i) all the exposed men could be followed to (say) the end of 1984, (ii) the investigators could present their data in comparable ways, taking account of duration of employment and time since first employment and presenting data separately for men first employed before (say) 1965 and between 1965 and 1974, and (iii) estimates could be made of the effect of correcting the results for each group of employees for the locality in which they lived and worked.

Hazards to the general population

As vinyl chloride has been proved to cause cancer in man and is a mutagen in laboratory experiments, it must be presumed that even the minute doses that escaped into the general environment from production plants or (in the early days of manufacture) from PVC materials will have caused some risk of cancer to the general public. These risks must, however, have been very small, as air concentrations of vinyl chloride, even within a kilometer of plants handling vinyl chloride, used to be (in or around 1975) of the order of 10 to 40 ppb (1, 3, 15), and this level is about one-ten thousandth of the concentration that has caused an occupational hazard. It is obvious, therefore, that it would be impossible to detect the risk of any cancer that might be produced by vinyl chloride other than a risk of angiosarcoma of the liver, as it has proved so difficult to detect any other risk among men who were exposed occupationally. The position with regard to an-

giosarcoma of the liver is different. This disease is normally so rare that, in the absence of specific exposure to one of the known causes (vinyl chloride, thorium dioxide, and arsenic in pesticides and medicines), the annual incidence is on the order of $1—2 \cdot 10^{-7}$ (5, 8).[6] In these circumstances the discovery of even one case in a man living close to a factory in which vinyl chloride was used in the days before exposure was tightly controlled may be regarded as presumptive evidence of the effect of environmental pollution.

Several surveys have been undertaken to determine whether any such cases have occurred. Saric et al (43) and Elinder & Pershagen (13) sought for cases in the vicinity of plants handling vinyl chloride in Yugoslavia and Sweden and found none. In Holland Dalderup et al (11) found eight confirmed cases not attributable to thorotrast or arsenic and could trace "no contact with vinyl chloride," but they made no specific mention of the patient's place of residence. Baxter et al (3) found 14 confirmed cases in Great Britain over a 12-year period, one of which was in a man who had lived half a kilometer from a PVC manufacturing plant, and, in New York State over an 18-year period, Brady et al (5) found 19 cases that could not be attributed to any known cause, five of which were in people living within a mile of plants manufacturing or using vinyl chloride. The overall incidence rates in these last two studies were not unduly high, but the occurrence of as many as six cases among people living so close to manufacturing plants is surprising. Brady and his colleagues, moreover, compared their series of patients with matched referents and found that none of the referents lived equally close to a plant. Two of these six neighborhood cases (one in England and one in New York State) cannot be attributed to environmental pollution with vinyl chloride, as the men who developed the disease had lived near the plants for six and eight years, respectively, before developing the disease, and this period is too short to allow for the necessary latency. The other four cases, however, all occurred after 15 or more years of local residence, and the discovery of these cases strongly suggests that pollution of the environment around plants manufacturing VCM or PVC may have caused a minute hazard to the general public.

Current concentrations around plants handling vinyl chloride are certainly much lower than those reported previously by the US Environmental Protection Agency. Recent British measurements made within a few hundred meters of the VCM areas have given average values below the daily limit of detection (5 ppb) for three of five plants, the readings at the two others being 20 ppb (100 m outside the boundary fence) and 88 ppb (just inside it) (47), although substantially higher values were recorded on two occasions associated with putting one plant into operation and with an accident at the other. According to any reasonable criterion the hazard to the general public (if there is any at all) must be negligible (42).

No other hazard to the general population, other than a hazard of cancer, can reasonably be postulated.

[6] The figure of $1.4 \cdot 10^{-8}$ cited by Heath et al (21) seems to have been a misprint for $1.4 \cdot 10^{-7}$.

Summary

This paper reviews (i) the possible effects of vinyl chloride on the personal health of men exposed by virtue of their occupation (other than the early effects of the very high concentrations to which men were exposed when the industry was first developed — unconsciousness, cardiac arrhythmia, and the characteristic "vinyl chloride illness") and (ii) the carcinogenic effects that might conceivably be observed in the general population as a result of the widespread distribution of vinyl chloride as a pollutant. The possibility that vinyl chloride might act as a teratogen or might cause mutations in the germ cells has not been examined, as the little evidence that has been adduced relating to such possible effects has been reviewed elsewhere and the conclusion was reached that no such effects have been demonstrated.

Many groups of workers exposed to vinyl chloride in the manufacture of VCM or PVC have been studied since the carcinogenic potential of vinyl chloride was first recognized. Some results have shown that occupational exposure can cause angiosarcoma of the liver, and others have suggested that it may cause several other types of cancer as well. The actual situation can be determined only in an examination of all the evidence, especially the combined results of those studies that include a substantial proportion of observations on men more than 25 years after their first exposure and cover a long enough period for more than 10 % of the employees to have been expected to die.

The results of four studies can be usefully combined for this purpose. They are two national studies, one from the US and the other from the UK, and two studies of employees in one plant in Canada and two plants in Italy. The results of other studies from the Federal Republic of Germany, Norway, Sweden, Italy, France, and Japan can be used only to provide supplementary information. The many earlier reports of exposed workers in the US and the UK concern men covered more completely in the two recent national studies, and their results serve only as sources of hypotheses.

Minor criticisms can be made of three of the four most useful studies. They do not seriously affect the value of the results, except that allowance has to be made for the failure to determine the cause of 6.3 % of the deaths recorded in the US study. Three of the studies use national rates to estimate the numbers of deaths that might have been expected to occur in the absence of any special occupational hazard, and the fourth (Canadian) uses rates for the province in which

the plant was situated. It must, therefore, be kept in mind that the rates used may not have been wholly appropriate for the localities in which the plants were situated. This circumstance is potentially important for the US study, which covered workers in 37 plants, 22 of which were situated in the southern part of the country. The other less informative studies are, for the most part, open to more serious criticism, and the value of each set of results needs to be assessed separately in relation to each disease.

The combined results of the four principal studies show that the SMR values, reflecting the ratios between the numbers of deaths observed and those expected in the absence of an occupational hazard multiplied by 100, have been (i) 77 for accidents and other violence, (ii) 84 for diseases other than cancer, and (iii) 102 for cancers other than cancer of the liver. All these results are what might be anticipated for an industry devoid of any specific occupational hazard. The low ratio for diseases other than cancer reflects the "healthy worker effect," which results from the selection process that inevitably excludes some of the less healthy members of the population from industrial employment and is compatible with a higher ratio for cancer, as the mortality from cancer is not normally subject to such an effect, apart from the first two or three years immediately following the start of employment.

The mortality from cancer of the liver was nearly seven times that expected. Most of the 51 excess deaths were known to be due to angiosarcoma, even though this diagnosis was not recorded on the death certificate. The excess corresponds closely with the 49 deaths due to angiosarcoma reported to the International Register of Angiosarcoma Cases as occurring in employees of the plants concerned during the periods under observation. All the men who developed the disease were likely to have been exposed to concentrations of vinyl chloride of several hundred parts per million or more.

Three other types of cancer which have been suggested to occur as a result of exposure to vinyl chloride are cancers of the lung, brain, and lymphatic and hematopoietic systems. The combined data for the mortality from respiratory cancer fail, at first sight, to support the hypothesis regarding lung cancer (SMR 97). Higher ratios for lung cancer have, however, been observed consistently in the subgroups in which the effect of an occupational hazard would be most likely to be seen (that is, men employed for more than 10 years, exposed to higher than average concentrations, or observed more than 20 years after first exposure). In two of the supplementary studies it was also noted that the mortality from lung cancer was specifically increased among the most heavily exposed workers. The combined data show small excesses in the mortality from cancers of the brain and of the lymphatic and hematopoietic systems. The excesses are, however, not statistically significant, and there is nothing to suggest that they are occupational in origin. An exception is the observation of an increased mortality from cancers of the lymphatic and hematopoietic systems in the supplementary study from the Federal Republic of Germany.

Two types of cancer were reported to be in excess in the Norwegian study, namely, thyroid cancer and melanoma. The significance of this finding is difficult to assess because very little information about these cancers has been provided by other studies.

Suggestions that vinyl chloride might cause cancers of the digestive tract have failed to account for the contribution of angiosarcoma of the liver. When this disease is excluded, the mortality from digestive tract cancer decreases to below the average (SMR 82 for the four principal studies).

A small excess mortality from the heterogeneous group of "other cancers" in the combined results of the four principal studies was statistically marginally significant (83 deaths against 65.25 expected, $P < 0.05$). Some of the excess was likely to have been due to the misclassification of angiosarcomas as secondary cancers of the liver or carcinomatosis, site unknown.

The following three nonmalignant causes of death have required special examination: cirrhosis of the liver because of damage to the liver in "vinyl chloride illness," myocardial infarction (from analogy with the effect of other halogenated hydrocarbons and because of some observations from Swedish PVC fabricators), and nonmalignant respiratory disease because of changes in lung function and the radiographic appearance of the lungs observed in men exposed to PVC dust. Far from being raised, the mortality from cirrhosis of the liver was less than expected in the three principal studies and in one of the two supplementary studies which gave separate figures for the disease (SMR values of 69, based on 46 deaths, and 82, based on 15 deaths), while in the other supplementary study the increase was trivial.

Data for myocardial infarction have not been reported separately. But myocardial infarction accounts for most of the deaths attributed to ischemic heart disease, and there is no evidence that either ischemic heart disease or cardiovascular disease as a whole was unduly common (SMR values of 90 and 92, respectively) or related to occupational exposure.

The data for the third category of nonmalignant disease (nonmalignant respiratory disease) are confusing, because the two large national studies give conflicting results. The combined data for the four principal studies show the low mortality that is commonly found in healthy industrial populations (SMR 80). This figure hides, however, an increased mortality from chronic obstructive lung disease (SMR 120), which includes emphysema and is due to a grossly increased mortality attributed to emphysema in the US study (SMR 193). The corresponding mortality in the British study, which was preferentially described as due to bronchitis, was less than expected (SMR 82), as was the mortality from pneumonia (SMR 50) and other res-

piratory diseases (SMR 46) in the US study. There is no consistent evidence that the mortality from emphysema or bronchitis was specifically occupational, and it seems possible that the reported excess in the US study was an artifact due to nosological difficulties with the use of the seventh revision of the ICD.

Review of the massive data now available on the long-term health of men occupationally exposed to vinyl chloride leads to two clear conclusions. First the men have experienced a specific hazard of the normally extremely rare angiosarcoma of the liver. Approximately 1 in 335 of the men exposed in the 49 plants studied died of the disease, and approximately 2 % of the observed deaths were attributed to it. In the course of time the numbers of cases of angiosarcoma must be expected to increase two to three times. Second, the mortality from all other causes has been typical of that of normally healthy industrial workers. If any hazard has existed, its effect has been small.

The data provide no reason to think that any hazard other than one of cancer has been overlooked. It is, however, still difficult to decide whether vinyl chloride produces small risks of cancer, compared to those due to nonoccupational causes, at sites other than the liver, and, if so, whether, in total, these risks might cause almost as many deaths as angiosarcoma of the liver.

There is too little evidence either to confirm or refute the suggestion that vinyl chloride might cause melanoma or cancers of the thyroid, brain, and lymphatic and hematopoietic systems. None of the small excesses that have been recorded point specifically to an occupational hazard, apart from that attributable to cancers of the lymphatic and hematopoietic systems in the German study reviewed, and most are likely to be the sort of chance effect that is certain to be observed when many types of cancer are examined in many different studies.

The lack of any increased mortality from lung cancer in the combined results of the four principal studies reviewed does not exclude the possibility that there may have been a small occupational hazard of developing the disease, as geographic variations in the incidence of the disease throw doubt on the validity of using national rates for estimating the expected numbers of deaths. The greater mortality in groups of workers who would be more likely to show an occupational hazard than other groups suggests that a small hazard may have existed. The evidence is, however, weak, and the existence of a hazard has not been proved.

Clearer answers to some of the questions that have been posed in this review might be obtained if the various groups of investigators could present their results in more appropriate and comparable ways.

As vinyl chloride is a mutagen in laboratory experiments and a proved human carcinogen, the minute doses that have escaped into the general environment as pollutants must be presumed to have caused comparably minute risks to the general public. No such risk could possibly be detected, other than one of angiosarcoma of the liver which is normally an extremely rare disease. Several surveys have sought evidence of the existence of such an effect, and suggestive evidence that such an effect may have occurred at a time when environmental pollution was much greater than it is now has been found in one.

References

1. Air Products and Chemicals, Inc. Comments on the proposed standard for vinyl chloride. Letter to DR Goodwin, Environmental Protection Agency, Washington, DC 23 September 1976. (Cited in an unpublished report by Barr to Air Products and Chemicals, Inc, in 1981).
2. Bauer ME, Teckman MS, Kennedy TP. Pulmonary function and respiratory symptoms in polyvinyl chloride fabrication workers. Am Rev Respir Dis 131 (1985) 203—208.
3. Baxter PJ, Anthony PP, MacSween NM, Scheuer PJ. Angiosarcoma of the liver in Great Britain, 1963—73. Br Med J 2 (1977) 919—921.
4. Belli S, Bertazzi PA, Comba P, Foa V, Maltoni C, Marsina A, Pirastu R, Regianni A, Vigotti MA. Indagine sulla mortalita dei produttori di PVC in Italia: Disegno dello studio e primi risultati. Cancer Lett (in press).
5. Brady J, Liberatore F, Harper P, Greenwald P, Burnett W, Davies TN, Bishop M, Polan A, Vianna N. Angiosarcoma of the liver: An epidemiologic survey. J Natl Cancer Inst 59 (1977) 1383—1385.
6. Buffler PA, Wood S, Eifler C, Suarez L, Kiliane DJ. Mortality experience of workers in a vinyl chloride monomer production plant. J Occup Med 21 (1979) 195—203.
7. Byren D, Engholm G, Englund A, Westerholm P. Mortality and cancer morbidity in a group of Swedish VCM and PVC production workers. Environ Health Perspect 17 (1976) 167—170.
8. Byren D, Holmberg B. Two possible cases of angiosarcoma of the liver in a group of Swedish vinyl chloride workers. Ann NY Acad Sci 246 (1975) 249—250.
9. Cooper WC. Epidemiologic study of vinyl chloride workers: Mortality through December 31, 1972. Environ Health Perspect, 41 (1981) 101—106.
10. Creech JL, Johnson MN. Angiosarcoma of liver in the manufacture of polyvinyl chloride. J Occup Med 16 (1974) 150—151.
11. Dalderup LM, Freni SC, Bras G, Bronckhurst FB. Angiosarcoma of the liver. Lancet 1 (1976) 246.
12. Duck BW, Carter JT, Coombes EJ. Mortality study of workers in a polyvinylchloride production plant. Lancet 2 (1975) 1197—1199.
13. Elinder CG, Pershagen G. Pilot study concerning the mortality in Njurunda Community. Swedish Nature Conservancy Board, 1978. (Cited in an unpublished report by Barr to Air Products and Chemicals, Inc, in 1981).
14. Environmental Health Associates. An update of an epidemiological study of vinyl chloride workers 1942—82: Final report to the Chemical Manufacturers Association. Environmental Health Associates, Oakland, CA 1986.
15. Environmental Protection Agency. Standard support document and environmental impact statement: Emission standard for vinyl chloride. Environmental Protection Agency, Washington, DC 1975. (EPA 450/2-75-009).
16. Equitable Environmental Health. Epidemiological study of vinyl chloride workers: Final report to Manufacturing Chemists Association. Rockville, MD 1978.

17. Falk H, Telles NC, Ishak KG, Thomas LB, Popper H. Epidemiology of thorotrast-induced hepatic angiosarcomas. Environ Res 18 (1979) 65—73.
18. Fiechtner J, Reyes C, Rentmeester K, et al. Epidemiologic notes and reports: Angiosarcoma of the liver — Wisconsin. Morb Mortal Wkly Rep 25 (1976) 57—58.
19. Forman D, Bennett B, Stafford J, Doll R. Exposure to vinyl chloride and angiosarcoma of the liver: A report of the register of cases. Br J Ind Med 42 (1985) 750—753.
20. Fox AJ, Collier PF. Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain. Br J Ind Med 34 (1977) 1—10.
21. Heath GW, Falk H, Creech JL. Characteristics of cases of angiosarcoma of the liver among vinyl chloride workers in the United States. Ann NY Acad Sci 246 (1975) 231—236.
22. Heldaas SS, Langard SL, Andersen A. Incidence of cancer among vinyl chloride and polyvinyl chloride workers. Br J Ind Med 41 (1984) 25—40.
23. International Agency for Research on Cancer. Some monomers, plastics and synthetic elastomers and acrolein. Lyon 1979, pp 377—438. (IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, volume 19).
24. Jones DP, Smith PM. Progression of vinyl chloride induced hepatic fibrosis to angiosarcoma of the liver. Br J Ind Med 39 (1982) 306—307.
25. Jones RD. A mortality study of vinyl chloride monomer workers employed in the United Kingdom in 1940—1984. Scand J Work Environ Health (in press).
26. Lilis R, Anderson H, Miller A, Selikoff I. Pulmonary changes among vinyl chloride polymerisation workers. Chest 2 (1976): suppl, 299—305.
27. Lloyd MH, Gauld S, Copland L, Soutar CA. Epidemiological study of lung function of workers at a factory manufacturing polyvinyl chloride. Br J Ind Med 41 (1985) 328—333.
28. Maltoni C, Ciliberti A, Gianni L, Chieco P. Vinyl chloride carcinogenesis: Current results and perspectives. Med Lav 65 (1974) 421—444.
29. Maltoni C, Lefemine G. Carcinogenicity bioassays of vinyl chloride: Current results. Ann NY Acad Sci 246 (1975) 195—218.
30. Maltoni C, Lefemine G, Ciliberti A, Cotti G, Carretti D. Experimental research on vinyl chloride carcinogenesis. In: Maltoni C, Mehlman MA, ed. Archives of research on industrial carcinogenesis. Volume 2. Princeton Scientific Publishers, Princeton, NJ 1984.
31. Marsteller HJ, Delbach WK, Muller R, Gedigk P. Unusual splenomegalic liver disease as evidenced by peritoneoscopy and guided liver biopsy among polyvinyl chloride production workers. Ann NY Acad Sci 246 (1975) 95—134.
32. Marsteller HJ, Delbach WK Muller R, Juhe S, Lange CE, Rohner HG, Veltman G. Chronisch-toxische Leberschäden bei Arbeitern in der PVC-Produktion. Dtsch Med Wochenschr 98 (1973) 2311—2314.
33. Masuda Y. Long term mortality study of vinyl chloride and polyvinyl chloride workers in a Japanese plant. Arch Ind Hyg Toxicol 30 (1979): suppl, 403—409.
34. Mirkova E, Mihailova A, Nosko M. Embriotakrichno i teratogenno destuige no vinilkhloride. Khig Zdraveopaz 21 (1978) 440. (Cited in an unpublished report by Barr to Air Products and Chemicals, Inc, in 1981).
35. Molan I, Molan G, Holmberg B, Elofsson S, Holmund L, Moosing R, Westerholm P. Mortality and cancer rates among workers in the Swedish PVC processing industry. Environ Health Perspect 41 (1981) 145—151.
36. Monson RR, Peters JM, Johnson MN. Proportional mortality among vinyl-chloride workers. Lancet 2 (1974) 397—398.
37. Nakamura K. A mortality study of vinyl chloride workers in Japan. Sangyo Ika Diaguka Zasshi 5 (1983): suppl, 49—57.
38. Nicholson WH, Henneberger PK, Tarr D. Trends in cancer mortality among workers in the synthetic polymers industry. In: Industrial hazards of plastics and synthetic elastimers. Liss, New York, NY 1984, pp 65—78.
39. Nicholson WJ, Hammond EC, Seidman H, Selikoff IJ. Mortality experience of a cohort of vinyl chloride-polyvinyl chloride workers. Ann NY Acad Sci 246 (1975) 225—230.
40. Ott MJ, Langner RR, Holder PB. Vinyl chloride exposure in a controlled industrial environment. Arch Environ Health 30 (1975) 333—339.
41. Pierre C, Tassignon JP, Pernin H, Spelkens J. Etude de la mortalite chez des travailleurs exposes au chlorure de vinyle. Arch Mal Prof Med Trav Secur Soc 40 (1979) 1131—1145.
42. Royal Society Study Group. Risk assessment: Report by a study group. Royal Society, London 1983.
43. Saric M, Kukcar Z, Zorica M, Gelic J. Malignant tumors of the liver and lungs in an area with a PVC industry. Environ Health Perspect 17 (1976) 189—192.
44. Soutar CA. Epidemiological study of respiratory diseases in workers exposed to polyvinyl chloride dust. Thorax 35 (1980) 644—652.
45. Tabershaw IR, Gaffey WR. Mortality study of workers in the manufacture of vinyl chloride and its polymers. J Occup Med 16 (1974) 509—518.
46. Thériault G, Allard P. Cancer mortality of a group of Canadian workers exposed to vinylchloride monomer. J Occup Med 23 (1981) 671—676.
47. Turner CA, Payne AP, Bushby BR. Determination of ambient levels of vinyl chloride monomer (VCM) around manufacturers in the UK: Part 7. Warren Spring Laboratory, Department of Trade and Industry, Stevenage (United Kingdom) 1984.
48. Viola PL, Bigotti A, Caputo A. Ontogenic response of rat skin, lungs, and bones to vinyl chloride. Cancer Res 31 (1971) 516—519.
49. von Greiser E, Reinl W, Weber H. Vinyl-chlorid exposition und mortalität deutscher chemiearbeiter im vergleich zur mortalität nichtexponierter chemiearbeiter und PVC-verarbeiter. Zentralbl Arbeitsmed Arbeitssch Prophyl Ergonomie 32 (1982) 44—62.
50. Waxweiler RJ, Stringer W, Wagoner JK, Jones J, Falk H, Carter C. Neoplastic risk among workers exposed to vinyl chloride. Ann NY Acad Sci 271 (1976) 40—48.

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