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TWO NEW CASES OF LIVER ANGIOSARCOMA: HISTORY AND PERSPECTIVES OF LIVER ANGIOSARCOMA AMONG PLASTIC INDUSTRY WORKERS

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In this report of two new cases of liver angiosarcoma (ASL) among plastic industry workers, the authors present the history and perspectives of this problem. The first cases of ASL have been registered since 1974, and in 1984, the European register of angiosarcoma was founded. In this register, 11 cases of ASL and one case of haemangiopericytoma have been registered from Croatia, all from a single plastics plant near Split.

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Two new cases of ASL (in retired autoclave cleaners, who were exposed to a concentration of 500–1000 ppm vinyl chloride monomer (VCM) during the working process) in the same plant are presented. They were detected with combined techniques of ASL detection,

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2. Abbreviations: ASL, liver angiosarcoma; ppm, parts per million; VCM, vinyl chloride monomer

3. Key words: chemical carcinogens, liver angiosarcoma, vinyl chloride monomer.

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and both are still alive. The diagnoses have been histologically confirmed: one of them was surgically treated with segmental liver resection. The appearance of new cases of ASL confirms the perspective presented in the last report by the same authors.

INTRODUCTION

Rapid development of the plastic masses industry dates 50 years back to the commercial production of VCM, by which polymerization polyvinyl chloride, the basic substance for the manufacture of plastic masses, is obtained. Toxicity and carcinogenic potential of vinyl chloride monomer (VCM) were investigated by various authors who gave experimental (Viola, 1970; Maltoni, 1974) as well as epidemiological evidence (Creech and Johnson, 1974). From the appearance of the first case of ASL in 1974 until 1993, 173 cases of liver angiosarcoma (ASL) have been recorded in the register established in the European Association of Plastic Masses since 1984.

The appearance of ASL in the plastic masses industry has resulted in very strict regulations of the emission of VCM in the working area: previous regulations have been reduced to 1 part per million (ppm) of VCM in the working area (in 1974) and firms that could not satisfy these demands were closed down. That value has been accepted as the "one hit" model and is considered not to be dangerous to workers' health . Those regulations were not promptly accepted by the countries of Eastern Europe, and in Croatia, the old regulation about the emission of VCM of 75 ppm in the working environment was valid until recently. It is generally considered that the workers in this branch of industry were exposed to concentrations of VCM which ranged up to 500 ppm. On the basis of the measurements performed by the chemical-technological laboratory in the factory which is under our control, a concentration of VCM similar to the one reported in literature was established. The workers in the above mentioned factory were exposed to elevated concentrations of VCM until 1987, which resulted in various forms of liver lesions up to the onset of ASL. Old-fashioned technology and ignorance of noxious effects of the VCM radiation have resulted in a great number of ASL cases in that factory, placing it with its 12 registered cases of ASL among the first in the world. The knowledge of toxic and carcinogenic effects of VCM has led to the application of new technologies which include "area" and "personal" monitoring with permitted concentrations of VCM up to 1 ppm. It should be emphasized that all new cases of ASL are, in fact, consequences of exposure to VCM within the period of 1949–1987 when old-fashioned technology with extremely high concentrations of VCM was used. According to available data, concentration to which the workers in the industries of plastic masses in the United States and Europe were exposed in the period up to 1974 when the first cased of ASL were detected, amounted to 500 ppm of VCM in the working environment. The prognoses of the most eminent world authorities from this field are disastrous: in the next three decades 300 new cases of ASL can be expected in Europe and up to 1200 cases in the United States. In our conditions (on the basis of previous investigations) new cases can be predicted at the rate of 1 case per year. This has been confirmed in practice: two new cases of ASL have been registered since our previous report.

CASE REPORT

1. B.M., born in 1933, was working in close contact with VCM for twenty years, six years as a cleaner of autoclaves. Subject stopped working in 1976 because of a liver lesion. The average concentrations of VCM to which he was exposed amounted to about 500–1000 ppm. Several months before the admission to the clinic, he felt weakness and dull pains below the right costal arch, so he was sent to a combined systematic examination. Ultrasonography revealed a mixed tumor of the liver, about 15 cm in size, and the patient was sent to hospital treatment.

Physical examination at admission:
Mental and psychological status was normal. Subject's height was 175 cm and weight was 78 kg. The cardiopulmonary finding was normal: *RR* 120/80 mmHg. Abdomen was tender, slightly sensitive below the right costal arch. Subject's liver was enlarged by 4 cm, hard, of uneven surface. The spleen was not palpable, and the LS was negative.

Laboratory findings for B.M. were as follows:
SE was 10 mm/h, prothrombin time was 12.4 seconds, index 95%, urine was turbid, specific weight 1021, numerous amorphous urates, alkaline phosphatase 345 IU/1, LDH 1659 IU/1, total proteins 85.4 g/1, albumins 57.1%.

Globulin readings were:
$alpha_1$ 3.2%, $alpha_2$ 10,6%, beta 15.4%, and gamma 15.4%. ECG finding was normal. X-ray of the lungs was normal as was the gastroscopic finding.

Ultrasonography found the liver enlarged, of nonhomogenous echo structure, with signs of diffuse lesions, a mixed focal zone, a predominantly hyperechogenic structure (diameter 15 cm) with single islets of hypoechogenic structure registered in part of the right lobe. Gallbladder and ducts were normal. Pancreas, kidneys, and spleen were normal.

CT of the liver showed a clearly defined, encapsulated tumor structure, 16 cm in diameter, from high subdiaphragmal layers to the level of the *porta hepatis*, chiefly suggesting a primary tumor of the liver in the transition zone from the right to the left lobe. Other parts of the liver appeared nonhomogenous, without focal changes. Gallbladder, ducts, and pancreas appeared normal.

Angiograph of the superior mesenteric artery, *truncus coeliacus* by the right transfemoral approach, the catheter was placed into the superior mesenteric artery. This presented a normal angiographic finding.

In the second act, the catheter was placed into the *truncus coeliacus*: arcuated repression of the branches of the hepatic artery and branches of the right hepatic artery for the medial part of the right liver lobe could be seen. In the transitional phase, that area was less imbibed by contrast, while in the portal phase, an impression of repression of portal veins showed only blood. The surgeon decided that the tumor was not operable due to its size and position. A laparotomy was performed and a wedge-shaped specimen of the liver parenchyma removed and sent for

pathohistological analysis. The findings of the analysis showed the received material to be a yellowish nodular segment of the liver parenchyma. Histologically, the greater part of the specimen consisted of the liver parenchyma of disordered structure with multiplied connective tissue in the portal areas spanning the lobules. It was inflamed, infiltrated by mononuclear cells, while hepatocytes showed fatty vacuoles. On the margins of a small part of the specimen, there was vaguely defined tumoric tissue built up of a diffuse mass of moderately polymorphonuclear cells and having a large vesicular nucleus with marked nucleolus and meager cytoplasm. In several places, the tumor cells surrounded fissures. The major part of the tumoric tissue was necrotic and permeated with blood. Immunohistochemical dyeing on cytokeratin in the tumors' tissue was negative, while Vimentin as well as von Willebrant factor (VIII) were positive. Numerous mitoses were found in the tumor tissue, many of them pathological. In one greatly enlarged field of sight, there were up to 8 mitoses. Histological picture and immuno-histochemical dyeing pointed to ASL and initial cirrhosis (Figure 1). Because of the general condition of the patient and the inoperability of the tumor, the opinion of the oncologist was demanded. As the tumor was highly radio- and chemo-resistant, he suggested symptomatic therapy. The patient was discharged, but remains under continuous care of the hepatologist.

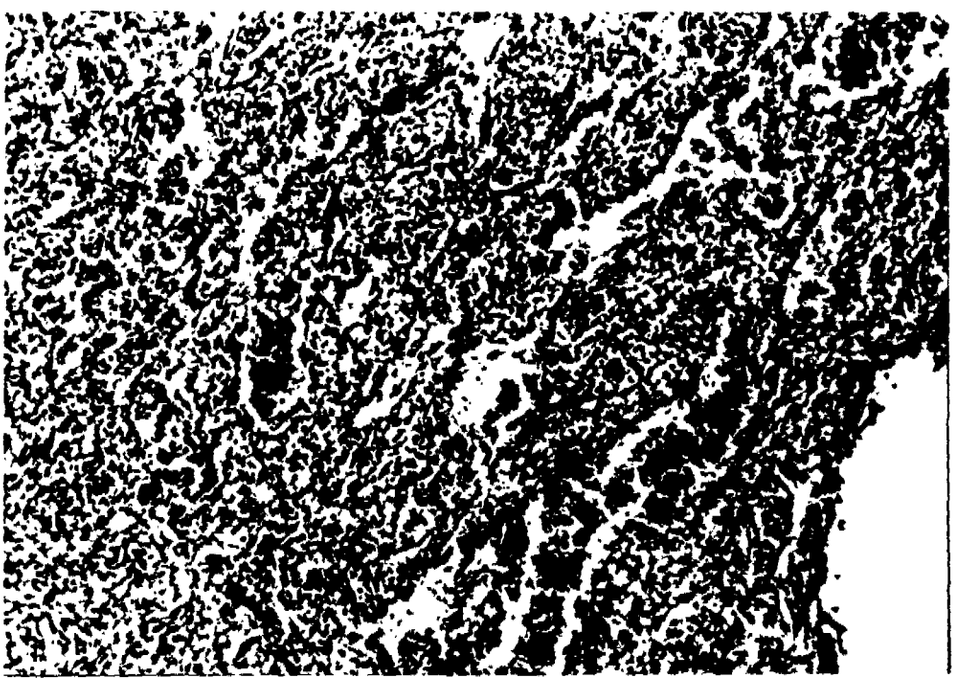

FIGURE 1. Histological presentation of ASL: Irregular blood vessels with dense series of tumor cells (HE, 78,7x).

2. G.M. born in 1927, retired in 1977, was working for 17 years in the production of VCM as a cleaner of autoclaves. Subject was exposed to average concentrations of 500–1000 ppm. Lesion of the liver was detected at retirement in 1977. He had increased blood pressure for years and had been treated with drugs and diuretics. A few days before admission he complained of dull pain in the epigastrium. Examined by the medical team for the detection of ASL, subject underwent ultrasonographic examination which disclosed a focal zone in the liver, so he was sent to hospital treatment. A moderate drinker, subject consumed up to half a liter wine daily.

Physical findings were as follows:
Mental and psychological status were normal. Subject's height was 175 cm, weight was 78 kg. His cardiopulmonary finding was adequate for his age: RR 165/95 mmHg, pulse 70/min.

The abdomen was tender, sensitive to palpation in the epigastrium and below the right costal arch. The liver was enlarged on account of the left lobe by about 6 cm, and was hard and of uneven surface. The spleen was not palpable.

Laboratory findings were as follows:
SE was 5 mm/h, prothrombin time was 14.9 seconds, with an index of 70%, INR was 1.26. Urine (sediment) contained numerous erythrocytes, mucus, some granulated cylinders, alkaline phosphatase 241 IU/l, gamma GT 142.9 IU/l, LDH 5097 IU/l, electrophoresis of proteins normal.

Ultrasonographic findings showed an enlarged liver of nonhomogenous echo structure with signs of diffuse lesion. In the left lobe, a focal zone of about 12 cm showed fields of hyperechogenic zones of mixed echostructure interspersed with islets of hypoechogenic zones. Gallbladder, ductus, and pancreas were normal. Kidneys showed preserved contours and were of adequate size.

CT of liver was as follows:
In the area of the left liver lobe, a spherical expansive structure with a diameter of 12 cm and with clearly defined contours could be seen bulging the surroundings and repressing the adjacent organs. The boundary with the surrounding hepatic parenchyma was clearly defined. It was composed of solid tissue with a value of 40 HU, and occasional hypodensic attenuations. After the application of intravenous contrast, a good imbibition of the contrast was obtained and the latter dispersed unevenly within the structure. The remaining part of liver showed preserved tissue of homogenous aspect with normal absorption values. Pancreas, kidneys, and spleen appeared normal. After the CT examination, a guided biopsy is performed which yielded bloody contents.

Cytological finding:
In markedly hypocellular smears of the liver punctate cells of peripheral blood, some clusters of hepatocytes, small clusters, and individual degeneratively changed cells of malignant aspect with large polymorphous hyperchromatic nuclei, prominent multiple nucleoli, and vaguely defined, pink cytoplasm could be seen, as well as a few degeneratively changed malignant bare nuclei.

The conclusion was malignant proliferation. The consulted surgeon decideed to operate with a previous angiography. By the right transfemoral approach, the catheter was placed into the truncus illiacus and an angiography was peformed after the application of the contrast. *Arteria lienalis* and *arteria hepatica* with their branches were visualized in the whole. *Arteria hepatica communis* continues into *arteria hepatica propria* which ramifies into *arteria hepatica dextra* and *ramus medius arteriae hepaticae*. The *arteria hepatica sinistra* was tense and arcuated, encompassing a structure of 10 x 12 cm which was in the projection of the vertebral column, i.e. on the border between the left and right lobes. In the subsequent arterial and venous phase, a whole series of residual islets of contrast could be seen. After the preparation, the patient was transferred to the Surgical Clinic where he underwent segmental resection during which the whole left lobe was removed with deep resections into the surrounding hepatic tissue.

Histological finding:
The received specimen was hepatic tissue of markedly disordered structure. The lobules were partitioned by connective bands and multiplied billiary ducts. Isolated regenerative nodules were also visible. There were large areas of necrosis and bleeding. Clusters of tumor cell nodes were composed of irregular vascular spaces lined with atypical endothelium with marked hyperchromatosis. The connective tissue was, in places, hypocellular and, in places, more prominent. Papillary formations built up of dense strains of tumor cells were visible. The conclusion was ASL (Figure 2).

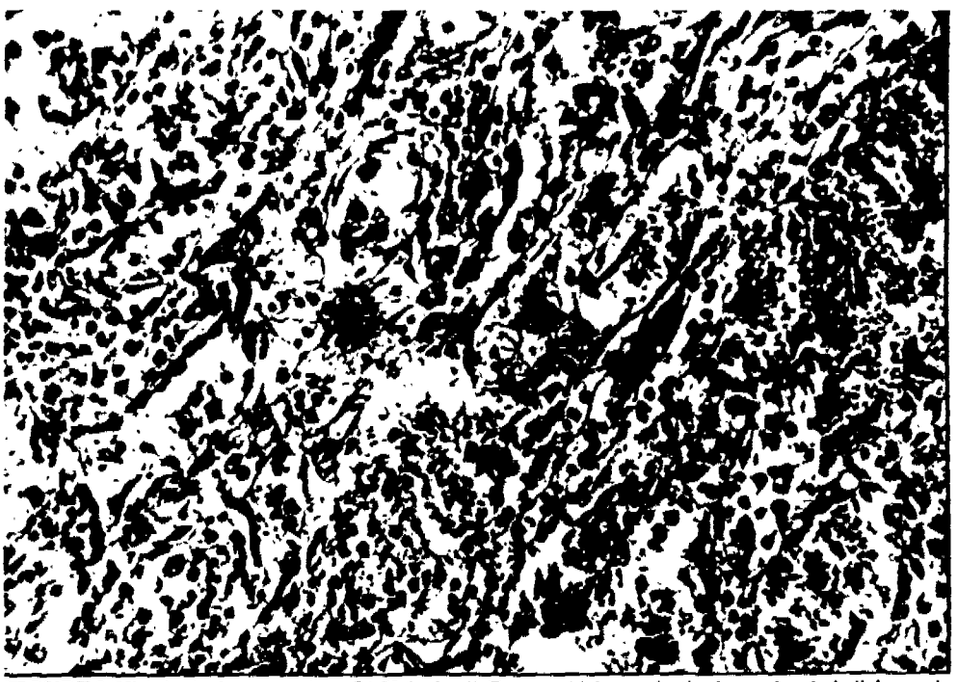

FIGURE 2. Histological presentation of ASL in detail: Tumor with hyperplastic changed endothelial vascular space (HE, 200x).

DISCUSSION

The appearance of ASL in workers from the industry of plastic masses has been controlled in the factory INA-Vinyl (former "Jugovinil", old VC-PVC plant near Split, Croatia) from one year after the first cases of ASL were reported in the United States. Since then, 9 cases of ASL and 1 case of haemangiopericytoma in the nearby branch of the secondary manufacture of plastic masses ("Jadranplastika" Trogir, old PVC plant near Split, Croatia) have been reported. All cases of liver tumor (twelve of them!) are associated with the emission of VCM and come from the above mentioned Dalmatian plastic masses industry. Since the appearance of the first case of ASL and the awareness of the interdependence between emission of VCM and onset of ASL, various measures of occupational safety have been introduced (transfer of autoclave cleaners to other jobs, safety masks and uniforms, cleaning of autoclaves by mechanical devices instead of by manual work, etc.), but new cases of ASL continued to appear. Since 1988 when the majority of ASL cases were discovered, the "combined technique of early detection of liver lesions," has been introduced, including anamnesis, physical examination, laboratory analyses, and ultrasound examination of the liver. The paradoxical fact in all this is that while all western legislations have strictly reduced the emission of VCM to the a maximum of 1 ppm in the working environment, the old Yugoslav standard from 1971 permitting the emission of 75 ppm of VCM was valid here all the time. The result of the previous exposure is the appearance of a large number of new cases of ASL, so that up to 1995, 12 ASL cases from Croatia were registered in the European ASL register kept at the Association of Plastic Manufacturers in Europe. The regulation by which the emission of VCM is reduced to the Western standards of 1 ppm in the working environment has only recently been defined in Croatia. Popper and Gedigkt have reported the hypothetical scheme of the onset of ASL in workers in the plastic masses industry. The exposure of hepatocytes to the VCM emission brings about the proliferation of sinusoidal cells which causes atypical hyperplasia up to ASL. ASL develops in the other way when the emission of VCM directly damages hepatocytes and the consequences are proliferation, formation of regenerative nodule, and the onset of tumors. The tumor typically presents a picture of wide vascular spaces and a system of anastomosed arterial canals lined with atypical endothelium with marked sarcomatous stroma. Both our patients presented the histological picture characteristic for ASL: endothelium in the form of dense rows of malignant cells with marked hyperchromatosis and polymorphism lining wide vascular spaces beside large bleeding zones. Both patients worked for a critically long period while exposed to high concentrations of VCM which probably gradually brought about the liver lesion (toxic hepatitis in the first; in the second, signs of fibrosis and cirrhosis) that would correspond to the hypothetical scheme of gradual onset of ASL (although direct onset of ASL is possible, without any grading). In both cases, the tumors developed gradually, practically without any symptoms, and were detected by the, "combined technique of early detection liver lesions," which includes the ultrasonography, on the assumption that ASL is extremely frequent among autoclave cleaners (1:100!). The tumors were, unfortunately, detected in an advanced stage, as it was the case of retired workers who came to the systematic check-up for the first time. Nevertheless, the tumor in the second patient could be operated, segmental resection of the liver was successfully performed, (there were no metastases) and he is in a satisfactory health condition. It is a fact that ASL in workers in the plastic industry is gradually becoming a danger of the past, due to strict observance of legal regulations about the VCM emissions. All future cases that will

appear in the next 20–30 years, will be due to the consequences of the, "cumulated concentrations of VCM," i.e., total concentrations of VCM to which the workers were exposed during the working process. According to mathematical models, that number will amount to approximately 300 new cases in West Europe and up to 1200 cases in the United States. Because of this, follow-up examinations of former workers from this branch of industry (former "Jugovinil") will be continued. This is because new cases can be expected during the next 15 years, which has been confirmed by the results of previous investigations. The appearance of ASL in workers in the plastic masses industry has been the greatest (unpremeditated!) world experiment which has proved the carcinogenicity of chemical compounds on human population and revealed unsuspected dangers from uncontrolled and unninvestigated chemical technologies to human health and the environment.

CONCLUSION

The appearance of new cases of ASL because of excessive concentration of VCM in the working environment even long after the cessation of exposure confirms the dimensions of the technical catastrophe, as well as the cumulative effect of chemical carcinogens. Their action can reasonably be compared with nuclear exposure and the protection is similar as well: avoidance of any concentrations of VCM in the working environment. Former autoclave cleaners with diagnosed ASL have chances to survive if they undergo segmental resection of the liver and if there are no metastases.

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Angiosarcoma of the liver in Great Britain in proximity to vinyl chloride sites

75-01-4

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Abstract

***Objectives*—To study the incidence of angiosarcoma of the liver in England and Wales 1979–86 and Scotland 1975–87. To investigate whether any non-occupational neighbourhood cases occurred near a vinyl chloride site.**

***Methods*—This is a geographical study of incident cases among the general population of Great Britain. Diagnosis of angiosarcoma of the liver was based mainly on the national cancer registry, the world register of cases among vinyl chloride workers, and the register of cases (including histological review) maintained by the Health and Safety Executive. Proximity (< 10 km) of residence to a vinyl chloride site was based on postcode of address at the time of diagnosis.**

***Results*—55 cases were ascribed to angiosarcoma of the liver in England and Wales with a further six cases in Scotland (annual incidence in Great Britain from all sources of around 1·4 cases per 10 million population). There were two cases with documented exposure to Thorotrast, and 10 cases among vinyl chloride workers. There were no vinyl chloride sites in Scotland. Among the 25 cases in England and Wales with histological diagnosis after review by a panel of pathologists, only 15 were confirmed as angiosarcoma, and one of the two Scottish cases after histological review was also confirmed. Overall, 11 cases ascribed to angiosarcoma were resident within 10 km of a vinyl chloride site; nine were vinyl chloride workers, one further case on histological review was not considered to have been correctly diagnosed as angiosarcoma, and the remaining case, confirmed as angiosarcoma, was employed at a vinyl chloride factory during the late 1950s, although not as a vinyl chloride worker.**

***Conclusion*—The incidence of angiosarcoma of the liver in Great Britain remains extremely rare. The one confirmed case in a non-vinyl chloride worker within 10 km of a site must nevertheless be presumed to have been exposed to vinyl chloride in the workplace. In the period of study, there were no confirmed non-occupationally exposed cases of angiosarcoma among residents living near a vinyl chloride site in Great Britain.**

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Keywords vinyl chloride; angiosarcoma; liver

Angiosarcoma of the liver is an extremely rare, rapidly fatal tumour. An association with occupational exposure to vinyl chloride monomer, used in the manufacture of polyvinyl chloride, was first reported in 1974[1]; since then a causal association has been established based on results of human occupational and animal experimental studies.[2–6] Associations with thorium dioxide (Thorotrast, which until the 1960s was used diagnostically as a radioactive contrast medium) and with arsenic exposure have also been described.[7–10]

Few studies are available on the incidence of angiosarcoma of the liver among the general population (see Doll[10] for a review). Baxter *et al* reported findings for Great Britain for 1963–73, later extended to 1977, and included one possible non-occupationally exposed neighbourhood case in the vicinity of a vinyl chloride plant.[7,8] In the present study, we describe the incidence of angiosarcoma of the liver in Great Britain for a later period with multiple sources of information to find possible cases. We were especially concerned with cases resident in the vicinity (within 10 km) of a plant that either handled vinyl chloride or used it for manufacturing. For those cases, we examined whether there was any evidence of occupational exposure to vinyl chloride, Thorotrast, or arsenic, and so whether or not any non-occupational neighbourhood cases had occurred.

Subjects and methods

Information on cases ascribed to angiosarcoma of the liver in Great Britain was sought from five sources (fig 1). Firstly, all cancer registrations coded to 155·0 (primary liver cancer) with histological code 9120 (angiosarcoma) were retrieved from the database of the Small Area Health Statistics Unit.[11–13] As histological coding for cancer registrations was not introduced until 1979 with the 9th revision of the international classification of disease (ICD-9), data for England and Wales refer to the period 1979–86 (the last year available at the time of study). In Scotland, cancer registrations before 1979 have been recoded to ICD-9, and so data were available for more years (1975–87). The registration details of cases in England and Wales were checked by the former Office of Population Censuses and Surveys (OPCS), and for Scotland by the Information and Statistics Division of the Scottish Health Service.

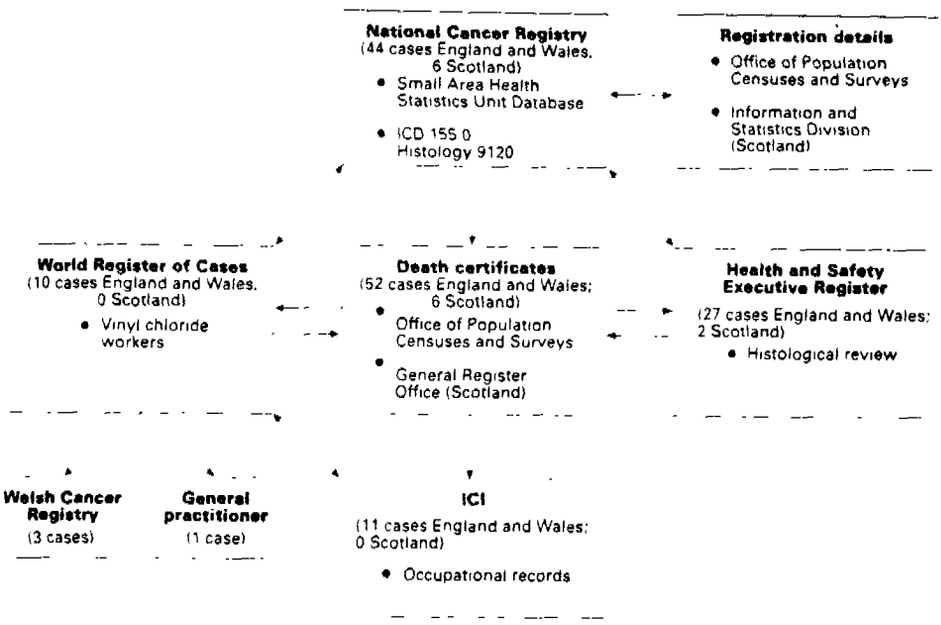

Figure 1 Sources of cases of angiosarcoma of the liver.

Secondly, copies of death certificates for the incident cases were sought from OPCS for cases in England and Wales and from the General Register Office (Scotland), and both primary and secondary causes of death were ascertained. The death certificates were also examined for mention of occupational exposure to vinyl chloride or industrial disease, and for exposure to Thorotrast or arsenic.

Thirdly, as a further check on cases, the non-confidential parts of the death certificates, including name, sex, address, date of birth, and date of death were abstracted. Extracts from a random sample of death certificates with primary liver cancer as underlying cause of death were included as controls. These were then sent to the Health and Safety Executive for checking against its register of cases, set up in 1974. The register includes histological review by a panel of pathologists of cases identified on the death certificate in Great Britain as angiosarcoma, as well as others identified from published case reports or notes from hospital pathologists or others.[7] Also, the register was checked for cases presenting with a diagnosis of angiosarcoma of the liver during the period of study that were missing from our lists, and details were sent to us (R Elliott, personal communication). Copies of death certificates (and controls) were also sought for those cases.

Fourthly, extracts of the death certificates for both cases and controls were sent to ICI Chemicals and Polymers to be checked against the occupational records. ICI has responsibility for both its own and former British Petroleum factories, which together contributed around 90% of workers (J Osman, personal communication) to the Health and Safety Executive's Employment Medical Advisory Service study of mortality among all vinyl chloride workers in Great Britain.[11]

Lastly, the United Kingdom entries on the World Register[11] of cases were scrutinised and the details compared with those on the database of the Small Area Health Statistics Unit. Comparison was made of sex, date of birth, date of death, age at diagnosis, and name of factory. We were also able to use the initials of the case (included on the world register) as names were available to us through the death certificates. Information on cases identified from the world register but not traced through the other sources was sought from the Welsh Cancer Registry (three cases) and, where necessary, through the local general practitioner (one case). Copies of death certificates (and controls) not otherwise obtained were retrieved and extracts sent for checking to the other information sources already described.

Information on the 12 vinyl chloride sites in Great Britain was obtained from the Department of the Environment (S Coster, personal communication), to include dates of operation, map grid references, and details of whether vinyl chloride was made, polymerised, used, or stored (fig 2). None of these sites was in Scotland. Cases were located by postcode of residence at the time of the diagnosis of cancer, or death, and the distance from the nearest vinyl chloride site was computed. Postcodes for three of the cases in England and Wales were missing from the database and were obtained from the death certificate or from OPCS.

Results

ENGLAND AND WALES

One duplicate registration was found. Overall, there were 55 cases ascribed to angiosarcoma in England and Wales 1979–86 (53 adults and two children (both female, ages 5 and 6)). Among adults, there were 37 men (ages 36–83 years; median 57 years) and 16 women (ages 25–80; median 59). Numbers of cases a year ranged from three (1986) to 10 (1983) (fig 3).

As expected, there was considerable overlap between sources (table 1). Of the total of 55 cases, 44 were identified on the national can-

Figure 2 Vinyl chloride sites in Great Britain.

cer registry. Copies of death certificates were obtained for 52 cases including 41 of the 44 cases that were found on the National Cancer Registry, and all 11 identified by ICI from its occupational records, 10 of which also appeared on the World Register for 1979–86. Of these 10 world register cases, only six were also found on the National Cancer Registry, although three further cases were on the Welsh Registry but had not been entered on to the national registry. Nine of the 10 World Register cases were also included among the 27 cases on the Health and Safety Executive register. Seventeen of these 27 cases were on the National Registry, and a further three—that is, nine minus six (table 1, last column)—were on the World Register but not on the National Registry. The remaining seven cases were identified only from the Health and Safety Executive register itself. Two of the 27 cases on the register had pathology recorded as "not yet known"; on panel review of the remaining 25 cases, 15 had the diagnosis of angiosarcoma confirmed (including the case known to ICI that was not on the world register: see discussion of table 2 later), and 10 were considered not to be angiosarcoma.

Death certificate diagnoses of haemangiosarcoma or angiosarcoma of the liver were recorded in 36 of the 52 cases for which a copy of the certificate was obtained, including one as a secondary cause of death, and two that mentioned Thorotrast exposure. Also, three cases were recorded as either haemangioendothelioma (one), haemangioendothelial sarcoma (one), or malignant haemangioma (one), considered to be synonymous with a death certificate diagnosis of angiosarcoma. One case with a death certificate diagnosis of haemangiocarcinoma and one with carcinomatosis were diagnosed as true angiosarcoma according to the Health and Safety Executive review panel, although the death certificate obtained for the case of carcinomatosis was possibly a mismatch as identifying details included on the register were scanty. One occupational case on the World Register had a death certificate diagnosis of hepatic fibrosis (and industrial disease was noted); the review panel considered that the diagnosis was not angiosarcoma (table 2). Death certificate diagnoses for the remaining 10 cases included hepatic tumour (one); hepatoma (two), chronic liver disease (one); angiocarcinoma of the liver (one), ischaemic heart disease and haemangioma of the liver (one); and four non-hepatic diseases, bronchogenic carcinoma (one), sarcoma of the kidney (one), melanoma (one), and carcinomatosis (one). None of the death certificates mentioned exposure to arsenic.

Table 2 lists all 11 cases in England and Wales ascribed to angiosarcoma during 1979–86 that were resident within 10 km of a vinyl chloride site (fig 2) at the time of the diagnosis of cancer. Nine of these cases were known vinyl chloride workers included on the World Register (the 10th World Register case was resident 11 km from the Barry factory). Eight were also on the Health and Safety Executive register, four with confirmed angiosarcoma, three were considered not to have angiosarcoma, and for one histology was recorded as not yet known.

Figure 3 Numbers of cases of angiosarcoma of the liver by year, England and Wales, 1979–86.

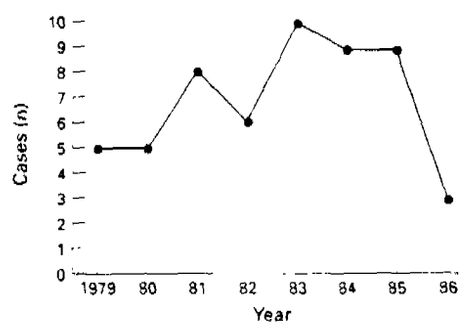

Table 1 Number of cases by information source, England and Wales, 1979–86 (55 cases in total)

	National Register*	Death certificate	HSE†	ICI	World Register
National Register	44	41	17	9	9‡
Death certificate	-	52§	27	11	10
HSE	-	-	27	10	9
ICI	-	-	-	11	10
World Register	—	—	—	—	10

*Primary liver cancer (ICD 155.0) and histology code 9120
†Health and Safety Executive Register
‡Three further cases on the World Register were also on the Welsh Cancer Registry (two coded as angiosarcoma of liver) but not on the National Registry
§Of the 55 cases in total, death certificates were untraceable for three cases on the National Registry
The total from each source is given along the diagonal, the rows and columns describe the overlap between sources

The remaining two cases were resident 6 km from a vinyl chloride site (table 2). The first, near the Baglan Bay plant, had no known history of exposure to vinyl chloride and histological review by the panel did not confirm angiosarcoma. The final case was confirmed by ICI as a former employee at the Barry factory, although working as a junior clerk and not a vinyl chloride worker for a period of five months during the late 1950s. The death certificate gave a diagnosis (after necropsy) of angiosarcoma of the liver and noted industrial disease. The Health and Safety Executive register recorded exposure to vinyl chloride and the review panel confirmed the diagnosis of angiosarcoma.

SCOTLAND

Scottish cases were included for consistency with earlier studies.[1,2] Six cases in Scotland were ascribed to angiosarcoma from 1975–87 (two men, four women); ages ranged from 59 to 81 years. Two cases occurred in 1982; the remainder (one each) in 1976, 1977, 1981, and 1984. Only two of the six cases were included on the Health and Safety Executive register (one confirmed as angiosarcoma on histological review). Death certificate diagnoses included three with haemangiosarcoma or angiosarcoma of the liver (one of which was also on the Health and Safety Executive register with a panel diagnosis considered not to be angiosarcoma). The three other death certificate diagnoses were primary liver cancer (confirmed as angiosarcoma by the review panel), carcinomatosis of the liver primary site undetermined), and diffuse poorly differentiated malignant lymphoma. None of the Scottish cases was known to ICI, or appeared on the World Register, and none mentioned Thorotrast or exposure to arsenic.

Discussion

We found 55 cases ascribed to angiosarcoma of the liver in England and Wales, 1979–86 and a further six cases in Scotland, 1975–87 giving a reported annual incidence in Great Britain of around 1·4 cases per 10 million population. These cases were based mainly on cancer registration, the world register of cases and the register maintained by the Health and Safety Executive. There were two cases with documented exposure to Thorotrast, none with exposure to arsenic, and 10 cases occurred in vinyl chloride workers. The incidence of around seven cases a year from all sources is similar to that reported for Great Britain during an earlier period (up to 1977),[2] although the sources of cases were different. In the previous study,[1,2] the primary source was death certificates supplemented by case reports and notifications from hospital pathologists and others. Among the 25 (of 27) cases in England and Wales included here from the Health and Safety Executive register with histological review by a panel of pathologists, only 15 were confirmed as angiosarcoma, a higher proportion than in the previous study[1,2] but based on a smaller percentage of the total number of cases. Only two of the six Scottish cases were included on the Health and Safety Executive register; one was confirmed as angiosarcoma on histological review.

We were particularly concerned in the present study to detect possible neighbourhood (non-occupational) cases in view of the theoretical risk of possible low level environmental hazard related to the operation of vinyl chloride sites, although the historical exposure to high concentrations of vinyl chloride in the workplace has been greatly reduced in recent years.[10] In the previous study in Great Britain, one possible neighbourhood case was described, with no known occupational expo-

Table 2 Angiosarcoma (ASL) cases within 10 km of a vinyl chloride (VCM) site, England and Wales 1979–86*

Site	Year of diagnosis	Age	Sex	Distance from site (km)	Exposure history	World Register	Death certificate	HSE register
Hillhouse	85	48	M	1	VCM	Yes	ASL Ind	Not ASL
Barry	79	65	M	2	VCM	Yes	ASL Ind	ASL
Hillhouse	79	58	M	3	VCM	Yes	ASL Ind	Not ASL
Barry	80	48	M	3	VCM	Yes	ASL Ind	¶
Barry	80	60	M	4	VCM	Yes		Not ASL
Barry	81	57	M	5	VCM	Yes	ASL Ind	ASL
Barry	85	57	M	5	VCM	Yes	ASL Ind	ASL
Barry	86	37	M	5	VCM	Yes	ASL Ind	-
Baglan Bay	79	63	M	6	†	No	ASL	Not ASL
Barry	83	42	F	6	‡	No	ASL Ind	ASL
Barry	84	37	M	8	VCM	Yes	ASL	ASL

*One further occupationally exposed case resident at 11 km
†Exposure status not known according to HSE register. Case not identified as a worker on ICI records
‡Recorded as having VCM exposure on HSE register. Worked at Barry plant as junior clerk but not occupationally exposed to VCM according to ICI records
§Hepatic fibrosis and industrial disease
¶Histology not yet known according to HSE register. Histology confirmed as angiosarcoma according to World Register
– = Not on HSE register. HSE = Health and Safety Executive, Ind = industrial disease recorded on death certificate