vinyl chloride carcinogenicity

VINYL CHLORIDE CARCINOGENICITY : AVAILABLE SCIENTIFIC EVIDENCE AND CONTROL MEASURES

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I) INTRODUCTION

The history of vinyl chloride (VC) carcinogenicity represented a highlight in the field of carcinogenesis for the lessons it gave, and it was a unique, exciting experience for all people involved: scientists engaged in experimental and epidemiological research, who produced the scientific evidence, and representatives of Governments, International Agencies, Industries and Unions, who prompted regulatory measures and preventive actions.

The aim of this report is to review that history, to summarize the present state of our scientific knowledge on VC carcinogenicity, give some references about the preventive measures which have been taken, and finally to underline and comment the major lessons we have learned.

II) GENERAL INFORMATION

Exhaustive reviews are available on the chemical and physical characteristics, production, uses and occurrence of VC, the exposed populations, the pathological effects of the monomer on humans and on experimental systems, and the regulatory preventive measures (Milby, 1978; Warren et al., 1978; IARC, 1979; Maltoni et al., 1984). Some basic, general information is given in Tables 1-5.

III) RESULTS OF VINYL CHLORIDE CARCINOGENESIS STUDIES

VC has been produced commercially since the end of the twenties, and it is one of the most important compounds of the plastic industry, and one of the petrochemical products synthetized in the largest quantity. However, for more than forty years, neither experimental research, nor epidemiological and clinical investigations were undertaken to study and assess its possible carcinogenic potential.

1) Viola's pioneering findings and other early observations.

A considerable number of studies were published at the end of the fifties and in the sixties, reporting the appearance of a unique syndrome, acro-osteolysis, on workers engaged in cleaning polivynil chloride (PVC) polimerization reaction vessels. This syndrome consists of bone changes (osteolytic and sclerotic lesions of the bones of the hands, mainly of distal phalanges, of larger bones and sacroiliac joints), skin changes (scleroderma-like lesions), and striking vascular changes associated with Raynaud-like phenomenon.

In 1967, P.L. Viola, a doctor at the Italian Solvay factory of Rosignano (Italy), attempted to produce acro-osteolysis on experimental animals. A group of 26 3-month-old male Ar/IRE Wistar rats was exposed to an atmospheric concentration of 30,000 ppm commercial grade VC (99% pure), for 4 hours/day, 5 days/week, for 12 months; the experiment was terminated at 54 weeks.

The outcome of this research was a surprise. Skin tumours developed in the submaxillary parotid region in all of the 17 surviving rats (14 epidermoid carcinomas, 2 mucoepidermoid carcinomas, 1 papilloma); in addition, lung tumours developed in 7 rats and osteochondroma in 5. No tumours were observed in 25 controls killed at un unstated time.

In his first report on the results of 12 months of exposure, Viola (1970 a) described metaplastic changes in bones, which he considered to be similar to human acro-osteolysis. The data on carcinogenic effects of VC were disclosed for the first time by Viola (Viola, 1970 b) at the 10th International Cancer Congress (Houston, 1970), and then extensively published in 1971 (Viola et al., 1971).

At the same time, at the Bologna Institute of Oncology, the cytological examinations of sputa from workers of VC-PVC industry, showed a high incidence of atypias of the cells of the respiratory epithelium (Maltoni et al., 1974).

Immediately after the Houston report, we communicated with Professor Viola, who kindly put at our disposal the manuscript of his extensive report, then in press, plus several slides of the tumours. On the basis of his results and material, we reached the conclusion that the tumours described as cutaneous were carcinomas originating from Zymbal glands, and that the pulmonary tumours were most likely metastases from Zymbal gland carcinomas. The neoplastic lung lesions were in fact morphologically similar to Zymbal gland carcinomas, and all were observed in animals bearing Zymbal gland tumours.

2) The Bentivoglio (BT) Project

On the basis of Viola's results and of the cytological observation on sputa, a systematic and integrated plan of experiments was started at the Bentivoglio (BT) Research Laboratories of the Bologna Institute of Oncology.

The project was sponsored by the Administration of the Bologna Institute of Oncology, and by a Consortium of European Industries: Montedison (Italy), Rhône-Poulenc (France), Solvay (Belgium) and ICI (Great Britain). It began in 1971 and lasted for twelve years.

The project studied the carcinogenic effects of VC administered by different routes, at different dose-levels, and for different periods, to animals of both sexes, and of various species, strain, and age.

The finalities of the BT project may be summarized as follows:

1) to detect the possible carcinogenic effects of VC;

2) to evaluate the full carcinogenic potentialities of VC on different organs and tissues;

3) to detect the most specific target organs prone to the carcinogenic effects of VC;

4) to provide data on the relationship between the dose of VC and the neoplastic response, with reference to different concentrations or daily dose, length of treatment, and number of treatments;

5) to quantify the carcinogenic potential of VC, with particular reference to low doses;

6) to study the effects of different routes of administration of the compound, namely: inhalation and ingestion which are the two main potential routes of human exposure, as well as intraperitoneal, subcutaneous injection, and transplacental (prenatal) exposure;

7) to investigate the effects of species, strain, sex and age, of the animals on VC carcinogenicity;

8) to provide information on the natural history of the most important tumours, with particular reference to liver angiosarcoma;

9) to produce any information, important towards the understanding of the pathogenetical mechanisms of VC carcinogenesis.

The plan of the BT Project, which included more than 7,000 animals, is shown in Tables 6-13.

Information on the test compound is given in Table 14.

All the animals were periodically weighed and submitted to control for the detection of gross lesions. They were kept under observation until spontaneous death.

Full necropsy was made on each animal, and systematic histopathology was performed on major organs and tissues, and, whatever the site, on all the pathological lesions (Table 15).

VC, on the basis of the BT Project, appeared to be a multipotential carcinogen (affecting different organs and producing a variety of tumours in all the tested species) in animals of both sexes and of different ages, at different doses, with different schedules of treatment, and by different routes of administration (inhalation, ingestion and via placenta, and possibly intraperitoneal and subcutaneous injection).

In the three treated species, the spectrum of VC correlated tumours varied from species to species, and included an ample range of neoplasias, namely:

- in rats (Sprague-Dawley and Wistar): malignant mammary tumours (particularly adenocarcinomas), Zymbal gland carcinomas, nephroblastomas, angiosarcomas, angiomas and fibroangiomas of liver and of other sites, hepatomas, encephalic neuroblastomas, forestomach papillomas and acanthomas, lung adenomas, and possibly cutaneous epithelial tumours;

- in mice: mammary carcinomas (adenocarcinomas), pulmonary adenomas (at high percentages with cellular atypias), angiosarcomas, angiomas and fibroangiomas of liver and of other sites, and possibly hepatomas, cutaneous epithelial tumours and forestomach papillomas and acanthomas;

- in hamsters: angiosarcomas of liver, forestomach papillomas and acanthomas, acustic duct epithelial tumours, and possibly extrahepatic angiomas and fibroangiomas, cutaneous epithelial tumours, melanomas, and lymphomas and leukaemias.

The range of the observed tumours, the relative incidence of the different types of tumours, the incidence of single type, and total neoplasias varied by changing different experimental factors such as: concentration or daily dose of VC, schedule of treatment with particular reference to the length of exposure, age, strain, and species of the animals used, and routes of administration of VC.

The data are summarized in Table 16.

There was a good correlation between dose and neoplastic response, particularly when total malignant tumours/100 animals were considered (Table 17).

The results of the experiments testing VC by ingestion are shown in Tables 18-23.

When VC was given by ingestion, the range of the tumours produced by the compound was narrower than following inhalatory exposure. The carcinogenic effect was mainly expressed by the high incidence of liver angiosarcomas (Tables 18, 21).

As shown following inhalatory exposure (Table 17), the neoplastic response was clearly correlated to daily doses (in the range 50-3.3 mg/kg body weight) (Exp. BT 11), also when the compound was administered by ingestion (Table 20).

The results of the experiments on Sprague-Dawley rats treated with different concentrations by inhalation for 52 weeks, and with different daily doses by ingestion for 52-59 weeks, have been submitted to statistical analysis, using the Fisher exact probability test (Maltoni et al., 1980) and the correspondence analysis (Tassignon, 1980).

Following statistical analysis using the Fisher exact probability test ($p \leq 0.05$):

a) the total number of cancer bearing animals per group were in excess at the doses indicated in Table 24;

b) of the nine tumours considered to be correlated to VC treatment, in the statistically analyzed experiments (mammary adenocarcinomas, Zymbal gland carcinomas, nephroblastomas, liver angiosarcomas, extrahepatic angiosarcomas, hepatomas, neuroblastomas, forestomach papillomas and acanthomas, and possibly cutaneous epithelial tumours), six appear significantly in excess, at least at one dose level and in one sex (Table 24).

The Fisher exact probability test at 95% confidence is probably not "sensitive" enough, under the tested experimental conditions. In our opinion, there are tumours at lower doses which must be considered biologically correlated to VC treatment (Table 25).

In the experiment BT 27, no specifically VC related tumours were observed in animals that were administered 0.03 mg/kg bw by ingestion (which, on body weight basis, would correspond to 2.100 mg in a man of 70 kg).

3) Other studies

Subsequent experiments, on a limited scale, confirmed the results of the BT project.

Groups of 100 male and 100 female CDI Swiss/ChR mice (age unspecified) were exposed to 2,500, 200, 50 ppm VC (purity unspecified) in air for 7 hours/day, 5 days/week for 9 months and were observed for an additional 9 months. Following 8 month's exposure, 49 untreated animals died with tumours, meanwhile no tumours were observed in 200 controls (100 females, and 100 males). VC was found to produce lung adenomas, liver angiosarcomas, and mammary carcinomas. A dose-related carcinogenic effect was evident (Keplinger et

Two groups, each of 12 male and 12 female, 3 month-old, NMRI outbred Albino mice, were exposed to 500 or 50 ppm VC in air for 6 hours/day, 5 days/week. The 500 ppm group was exposed for only 25 weeks (due to the poor condition of mice) and the 50 ppm group was exposed for 52 weeks, at which time the experiment was terminated. Groups of control animals were included in the experiments. Under these experimental conditions, VC caused, at high and low concentrations, pulmonary adenomas, extrahepatic angiosarcomas, and, at higher concentrations, an increase in mammary carcinomas, and one liver angiosarcoma (Holmberg et al., 1976).

Groups of 36 male and 36 female, 2-month-old, Albino CD mice were exposed to 1,000, 200 and 50 ppm VC (99.8% pure) in air for 6 hours/day, 5 days/week for 52 weeks; at that time, 70, 52, 46 and 38 animals respectively were still alive. Control animals were available. VC was found to cause lung adenomas, angiosarcomas of liver, extrahepatic angiosarcomas, and mammary carcinomas. A dose-related carcinogenic effect was evident for lung adenomas and liver angiosarcomas (Lee et al., 1977, 1978).

Groups of 36 male and 36 female, 2-month-old, CD rats were exposed to 1,000, 250, 50 and 0 ppm VC in air (99.8% pure) for 6 hours/day, 5 days/week for 12 months, at which time the surviving animals (72, 70, 58 and 51 respectively) were killed. Liver and lung angiosarcomas occurred in rats treated with 1,000 and 250 ppm. A dose-related carcinogenic effect was evident (Lee et al., 1977).

Groups of 62 male and 62 female Wistar rats were exposed to 5,000 and 0 ppm VC in air, 7 hours/day, 5 days/week for 52 weeks. Tumours were observed in liver (hepatocellular carcinoma and angiosarcoma), brain, ceruminous glands, and nasal cavities (Feron et al., 1979 b; Feron and Kroes, 1979).

Small groups of male, 5-week-old, CD1 Swiss/ChR mice were exposed to 6,000, 2,500 and 0 ppm VC in air for 5 hours/day 5 days / week for 5 and 6 months. Under these experimental conditions the animals were sacrificed between 2 to 37 days following the end of the treatment. VC was found to cause lung adenomas in 26 of the 27 treated animals. None of these tumours were found in the 16 controls. Light and electron microscpic studies suggested that neoplastic cell originate from type II alveolar epithelium via its hyperplastic form (Suzuki, 1978, 1981).

Hehir et al. (1981, and Unpublished Report with limited circulation) studied the effects of the exposure to several concentration (50,000, 5,000, 500 and 50 ppm) of VC vapour, administered 1 hour, once, on Fischer 344 rats, and in ICR mice. The same total dose, 5,000 ppm, was delivered in 10 (x 500 ppm) or 100 (x 50 ppm) times, for 1 hour/day, 5 days per week, on Fischer 344 rats, and in A/J mice. Animals of both sexes were used. The age of the animals at the start varied from 8 to 21 weeks. The animals were kept under observation up to 24 months (rats), and up to 20 months (mice). Interim sacrifices were performed at different periods of the experimental biophase. This study was sponsored by the Consumer Products Safety Commission (CPSC) (USA).

The most important results of this study are :

- the enhancement of total tumours in Fischer rats, following 10 and 100 1-hour exposure to 500 and 50 ppm respectively;
- the clear-cut enhancement of pulmonary tumours and of total tumours in ICR mice, following the exposure to 50,000 ppm for 1 hour;

- the enhancement of total tumours and of pulmonary tumours (also of adenocarcinomas) in A/J mice, following 10 1-hour exposures to 500 ppm, and of total tumours, following 100

1-hour exposures to 50 ppm.

Groups of male and female Sprague-Dawley rats, of different ages (6, 18, 32 and 52 weeks) were exposed to 940 ppm VC by inhalation, 7 hours/day, 5 days/week for 24 weeks. In each age group there were 110 to 128 males, and the same number of females. Control groups, which were not exposed to VC, consisted of the same number of males and females, in each age group (Groth et al., 1981). All animals died spontaneously, were sacrificed moribund, or were killed at schedule times (3, 6 and 9 months after initial exposure). The Authors summarized their results as follows: "The older the rats were when they were first exposed, the greater the incidence of angiosarcomas. The incidence of angiosarcomas in the four age groups (from youngest to oldest) in the exposed males, in the non-schedules sacrifice groups were: 0/37 (0%); 0/44 (0%); 3/45 (6.7%); and 13/55 (24%). Similarly, for the females, these incidences were: 2/38 (5.3%); 7/47 (15%); 23/49 (47%); and 11/54 (20%). Most of the angiosarcomas were highly anaplastic, primary tumours in the livers that metastasized to the lungs. Only one agiosarcoma was seen in all the control rats; that occurred in subcutaneous tissues. This study demonstrated that older adult animals (in the studied range of ages) and females are more susceptible to the angiosarcoma-inducing effects of vinyl chloride than young adult animals and males, respectively."

Four treatment groups (80 male Sprague-Dawley rats per group) were treated as follows: inhalation of 600 ppm VC, 4 hours/day 5 days/week for 52 weeks; VC, with the same regimen, and 5% ethanol in drinking-water (V/V) (the ingestion of ethanol was begun four weeks prior to inhalation of VC, and continued for life or termination of the study); ethanol, with the same regimen, and filtered air; and filtered air. The study lasted two and one-half years from the first VC exposure. Inhalation of VC induced liver angiosarcomas in 23% of the exposed animals;

ethanol in addition to VC inhalation increased the incidence to 50%; concomitant administration of VC and ethanol also produced an excess of hepatocellular carcinomas and lymphosarcomas. Ethanol, with or without VC, had a strong tumorigenic effect on the endocrine system. In this model system, ethanol appears to potentiate the carcinogenic response to VC (Radike et al., 1981).

IV) EPIDEMIOLOGICAL EVIDENCE

1) Liver angiosarcoma

Following the early 1973 results of the experiment of the BT project (Maltoni, 1974 a; Maltoni and Lefemine, 1974 a, b), in 1974, more than forty years after the introduction of VC in industry, Creech and Johnson (1974) reported for the first time an association of exposure to VC with cancer in man. Three cases of liver angiosarcoma were reported in men who were employed in VC-PVC industry, in a single VC polymerization plant in the USA. Further retrospective investigations showed that in previous years (precisely since 1955), workers exposed to VC had died for liver angiosarcoma, but, in absence of experimental indications, these cases were misdiagnosed and not correlated with VC exposure.

In the same and the following years, by reviewing medical records and pathological material, on the basis of clinical observations, and by systematic medical screening and epidemiological investigations, other liver angiosarcomas in workers exposed to VC were reported in the USA, as well as in other Countries (Forman et al., 1985).

At present 119 liverangiosarcomas have been reported in different countries (Table 26).

The high majority of liver angiosarcomas were observed in VC-PVC polymerization plants, and particularly among cleaners of PVC polymerization reaction vessels

2) Other tumours

An excess of tumours involving different organs and different histotypes (other than liver angiosarcoma) has been correlated to VC occupational exposure, starting from 1974 (Maltoni et al., 1984).

These tumours include: angiosarcomas of the duodenum, heart, kidney, and other sites, tumours of the brain and central nervous system (glioblastoma multiforme), large-cell undifferentiated carcinomas of the lung, lymphomas and leukemias, carcinomas of the biliary tract, carcinomas of the pancreas, mammary carcinomas in the women, carcinomas of the urinary tract, hepatocarcinomas, and malignant melanomas. The degree of evidence varies from tumours to tumours. The most evident correlation is found between VC exposure and tumours of the brain and central nervous system.

V) THE MILESTONES

The most important steps towards the knowledge of VC carcinogenicity, including specific oncological research and toxicological pertinent contributions, are listed in Table 27.

VI) THE MEASURES OF CONTROL

1) Work environment

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Until 1973 the Threshold Limit Value (TLV) (ceiling) for VC in work-place was 500 ppm or 1.300 mg/m^3. It has been claimed that TLV was in fact reduced to 250-200 ppm in American and European factories some years before. It must be pointed out, however, that during that period the concentration in work-place was not submitted to systemic controls, meanwhile, many engineers, workers and medical doctors reported that frequently the concentration level of VC in PVC polymerization unit reached the olphactory level (the not unpleasant odor of VC can be detected by someone at concentrations as low as 300 ppm, but other people cannot detect it until the gas reaches much higher concentrations).

The Occupational Safety and Health Administration (OSHA) issued for the USA an emergency standard limiting VC air level to 50 ppm, following the first experimental and epidemiological investigations that VC causes liver angiosarcoma and the Maltoni's report at OSHA (1974 b) that liver angiosarcomas were observed in animal exposed to VC at the concentration of 250 ppm. This standard was then lowered to Time-Weighed-Average (TWA) of 1 ppm, following the report that VC causes angiosarcoma in animals down to a concentration of 50 ppm (Maltoni and Lefemine, 1975).

At present in the USA, OSHA's health standards for exposure to air contaminants require that an employee's exposure to VC not exceeds an eight-hour time-weighed average of 2.6 mg/m^3 (1 ppm) in the work-place air in any eight-hour work shift of a forty-hour work week. During any work shift an employee's exposure may not exceed a ceiling concentration limit of 13 mg/m^3 (5 ppm), averaged over any period of 15 minutes or less (US Occupational Safety and Health Administration, 1974).

In August 1977, the value proposed by the Commission of the European Communities for the member Countries was 3 ppm over one year, for existing and future plants, with an "alarm-value" of 15 ppm.

Technological improvement in VC-PVC factories made it possible to fulfill the required standards.

2) Food.

The Commission of the European Communities adopted a level of 1 mg/kg (1 ppm) as the amount of VC which can be present in packaging, and 0.01 mg/kg (ppm) in foodstuffs packed in PVC (Commission of the European Communities, 1977, 1978).

The levels of the residues of VC in PVC used for food packaging and beverage containers, and therefore the possibility of migration of the monomer from PVC containers to food and beverages, have been progressively and sharply decreasing in the last ten years

In 1974 and 1975 the content of VC in the PVC walls of water, wine and edible oil containers and in the contained liquids was determined by Wolff (Clichy, France) and other (Dorlyl, BAP, BAP-Solvic, Rhone-Poulenc) laboratories. The sensitivity limit of the analytical methods was 5 ppm for VC in the walls of the containers, and 0.05 ppm in the liquids. The results of the analyses showed a level of VC in the walls ranging from not detectable level to 13 ppm. The content of VC in the liquids were below the level of the sensitivity of the methods.

In 1975 the content of VC in the walls of mineral water, wine and edible oil containers was again determined by Wolff Laboratories, with a method whose sensivity limit was in the order of 0.2 ppm. The results of these analyses showed that the VC contents were ranging from not detectable level up to 0.7 ppm.

In 1976 Wolff Laboratories analyzed the content of VC in several liquids (edible oils, vinegar, wine and mineral water) stocked in PVC (1975) containers, after 6 months of stockage. The sensitivity limit for VC in oil was 15 ppb and for VC in aqueous liquids 2-3 ppb. The content of VC varied from 15 to 30 ppb in oils, was 9 ppb in vinegar and wine, and varied from 2 to 3 ppb in mineral waters.

In 1985, with the same analytical method* in the same Wolff Laboratories, no VC was detected in natural mineral water (of different origins and types), spring water (of different sources), soft drinks of different types, red wines and edible oils of different types.

VII) CONCLUSIVE REMARKS

The experimental BT project, and the entire body of research (experimental, epidemiological, pathological, clinical, environmental) which followed on VC carcinogenicity, have brought for important specific information, progress, decisions and facts in the field of VC carcinogenesis and of occupational and environmental carcinogenesis in general.

* As specified by the EEC Commission DIRECTIVE 81/432/CEE, April 29th, 1981

1) The studies on VC carcinogenicity have led to the control of VC exposure, and hopefully the avoidance of additional cases of VC related diseases.

2) They demonstrated that experimental findings can be extrapolated to human pathology.

3) They have constituted a model for research protocols in the field of studies on environmental and occupational carcinogenesis, including a large part of the ones enclosed in the Good Laboratory Practice Acts, for long-term carcinogenicity bioassays.

4) They have promoted carcinogenicity studies of numerous chemically correlated compounds, to assess their potential risk.

5) They have stimulated national and international regulations and acts for the control of environmental toxic agents, encompassing the ones requiring pre-production testings.

6) They have contributed to the basic knowledge of factors and mechanisms in canc erogenesis.

7) Finally, VC carcinogenicity has brought forth an important lesson: the studies in the field of environmental and occupational carcinogenesis, particularly in industrialized countries, must no longer be considered a retroguard ancillary research, but rather they must represent an important component of the decision making processes which regulate the developmental trends of society.

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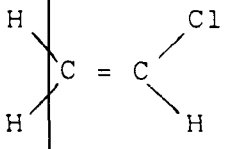
Table 1

VC : structural and molecular formulae and molecular weight



C_2H_3Cl

Mol. wt.: 62.5

Table 2

VC : production

Methods of production:	VC is produced commercially by : - halogenation of ethylene - addition of hydrogen chloride to acetylene
World production (1976):	10 million tons per year
Major geographical areas of production:	Western Europe, USA, Japan, Eastern Europe

Table 3

VC : uses

Major uses: production of the homopolymer, polyvinyl chloride (PVC) and copolymer resins (mainly vinyl chloride-vinyl acetate and vinyl chloride-vinylidene chloride copolymers)
Other uses: production of methyl chloroform
Miscellaneous uses (in the past): as a refrigerant, as an extraction solvent for heat-sensitive materials, in the production of chloroacetaldehyde, as an aerosol propellant, as an ingredient of drug and cosmetic products, and, in medicine, as an anesthetic

Table 4

VC : occurrence (1)

Natural sources:	it is not known to occur as a natural product
Workplaces :	where PVC, VC copolymer resins and VC, and other products containing VC are produced, used and stocked
Air :	- general atmosphere around the plants of VC-PVC
	- around incinerators
Water :	- effluent discharged by chemical plants
	- raw water
	- finished drinking-water
Food and drink (stocked in PVC containers) :	
	- butter and margarine
	- edible oils
	- alcoholic beverages
Other :	- new automobile interiors
	- cigarettes and little cigars
	- marijuana cigarettes

(1) IARC, 1979; Maltoni et al., 1984

Table 5

VC : data on biological effects relevant to carcinogenesis (1)

1) Toxicity studies

A) Experimental animals:

a) VC causes toxic effects on the liver of several experimental rodents (mice, rats and guinea pigs), and on the kidney of mice

b) VC produces hyperplasia of bronchiolar and alveolar epithelium, in mice

B) Humans :

a) VC causes acro-osteolysis

b) VC produces liver changes,consisting in hepatomegaly, conspicuous sub-capsular fibrosis, a non-pathognomonic progressive portal fibrosis, a border-line increase in intralobular connective tissue, dilatation of sinusoids, and focal stimulations of hepatocytes and of sinusoidal lining cells

c) VC causes interstitial fibrosis in the lung, and atypias of the cells of the respiratory epithelium

2) Genetic effects

A) Bacterial and yeast systems: VC is mutagenic after metabolic activation

B) Other systems: VC causes chromosomal aberrations and sister chromatid exchanges, in animals and human cells

(1) IARC, 1979; Maltoni et al., 1984

Table 6

BT Project on VC carcinogenicity. Exp. BT 1, 2, 6, 9, 15 : plan

Route of administration: inhalation. Test animals: Sprague-Dawley rats

Purpose: evaluation of the carcinogenicity of VC and of the effects of the concentrations (14) (basic experiments)

Experiment	Treatment			Animals							Duration of the experiment
	Route	Doses of VC	Duration	Species	Strain	Age (weeks)	No. M	No. F	No. Total	No. Per group	
BT1	Inhalation	10,000, 6,000, 2,500 500, 250, 50 ppm. Untreated controls: 0. Treated controls: vinyl acetate 2,500 ppm	4 hrs. daily, 5 days weekly, 52 weeks	Rat	Sprague-Dawley	13	240	240	480	60 M F	Life span
BT2	Inhalation	200, 150, 100 ppm, 0.	4 hrs. daily, 5 days weekly, 52 weeks	Rat	Sprague-Dawley	13	265	280	545	120-185 MF	Life span
BT6	Inhalation	30,000 ppm	4 hrs. daily 5 days weekly, 52 weeks	Rat	Sprague-Dawley	17	30	30	60	60 M F	Life span
BT9	Inhalation	50 ppm, 0.	4 hrs. daily, 5 days weekly, 52 weeks	Rat	Sprague-Dawley	11	200	200	400	300-100 MF	Life span
BT15	Inhalation	25, 10, 5, 1 ppm, 0.	4 hrs. daily, 5 days weekly, 52 weeks	Rat	Sprague-Dawley	13	300	300	600	120 M F	Life span

Table 7

BT Project on VC carcinogenicity. Exp. BT 3, 10 : plan

Route of administration: inhalation. Test animals: Sprague-Dawley rats

Purpose: evaluation of the effects of the length of exposure on VC carcinogenicity

Experiment	Treatment			Animals							Duration of the experiment
							No.				
	Route	Doses of VC	Duration	Species	Strain	Age (weeks)	M	F	Total	Per group	
BT3	Inhalation	10,000, 6,000 2,500 500, 250, 50 ppm, 0.	4 hrs. daily, 5 days weekly, 17 weeks	Rat	Sprague-Dawley	12	288	262	550	60-190 M F	Life span
BT10	Inhalation	10,000, 6,000 ppm, 0.	4 hrs. daily, 5 days weekly, 5 weeks; 4 hrs. daily, 1 day weekly, 25 weeks; 1 hr. daily, 4 days weekly, 25 weeks	Rat	Sprague-Dawley	11	469	480	949	120-229 M F	Life span

Table 8

BT Project on VC carcinogenicity. Exp. BT 5, 14 : plan

Route of administration: inhalation and transplacental. Test animals: Sprague-Dawley rats

Purpose: evaluation of the effects of age on VC carcinogenicity and prenatal VC carcinogenesis bioassay

Experiment	Treatment			Animals						Duration of the experiment
	Route	Doses of VC	Duration	Species	Strain	Age (weeks)	No. M	No. F	No. total	No. Per group
BT5	Inhalation	10,000, 6,000 ppm	4 hrs. daily, 7 days (from 12th to 18th day of pregnancy)	Rat	Sprague-Dawley	Breeders 13	-	60	60	30 F
	Transplacental					Embryos 12th day of pregnancy	37	49	86	32-54 M F
BT14	Inhalation	10,000, 6,000 ppm	4 hrs. daily, 5 days weekly, 5 weeks	Rat	Sprague-Dawley	Parents 21	-	12	12	6 F
						1 day	43	45	88	43-45 M F

Table 9

BT Project on VC carcinogenicity. Exp. BT 4001-4006 : plan

Route of administration: inhalation and transplacental. Test animals: Sprague-Dawley rats

Purpose: evaluation of the effects of length of exposure and age on VC carcinogenicity

Experiment	Treatment			Animals							Duration of the experiment
							No.				
	Route	Doses of VC	Duration	Species	Strain	Age (weeks)	M	F	Total	Per group	
BT4001 and 4006	Inhalation	2,500 ppm, 0.	4-7 hrs. daily, 5 days weekly, 76 weeks	Rat	Sprague-Dawley	Breeders 12	-	114	114	54-60 F	Life span
	Transplacental and inhalation		4-7 hrs. daily, 5 days weekly, 76 weeks			Embryos 12th day of pregnancy	281	273	554	120-307 M F	Life span
			4-7 hrs. daily, 5 days weekly, 15 weeks								

Table 10

BT Project on VC carcinogenicity. Exp. BT 7, 17 : plan

Route of administration: inhalation. Test animals: Wistar rats

Purpose: evaluation of the effects of the strain on VC carcinogenicity

Experiment	Treatment			Animals							Duration of the experiment
						Age	No.				
	Route	Doses of VC	Duration	Species	Strain	(weeks)	M	F	Total	Per group	
BT7	Inhalation	10,000, 6,000, 2,500, 500, 250, 50 ppm. Untreated controls	4 hrs.daily, 5 days weekly, 52 weeks	Rat	Wistar	11	220	-	220	30-40 M	Life span
BT17	Inhalation	1 ppm. Untreated controls	4 hrs. daily, 5 days weekly, 52 weeks	Rat	Wistar	13	250	-	250	120-130 M	Life span

Table 11

BT Project on VC carcinogenicity. Exp. BT 4, 8 : plan

Route of administration: inhalation. Test animals: Swiss mice and Syrian Golden hamsters

Purpose: evaluation of the effects of the species on VC carcinogenicity

Experiment	Treatment			Animals							Duration of the experiment
							No.				
	Route	Doses of VC	Duration	Species	Strain	Age (weeks)	M	F	Total	Per group	
BT4	Inhalation	10,000, 6,000, 2,500 500, 250, 50 ppm. Untreated controls.	4 hrs. daily, 5 days weekly, 30 weeks	Mouse	Swiss	11	260	250	510	60-150 M F	Life span
BT8	Inhalation	10,000, 6,000, 2,500 500, 250, 50 ppm. Untreated controls.	4 hrs. daily, 5 days weekly, 30 weeks	Hamster	Syrian Golden	11	268	-	268	30-62 M	Life span

Table 12

BT Project on VC carcinogenicity. Exp. BT 12, 13 : plan

Route of administration: endoperitoneal and subcutaneous injection. Test animals: Sprague-Dawley rats

Purpose: evaluation of the effects of the route of administration on VC carcinogenicity

Experiment	Treatment			Animals							Duration of the experiment
							No.				
	Route	Doses of VC	Duration	Species	Strain	Age (weeks)	M	F	Total	Per group	
BT12	Endoperitoneal injection	4.25 mg in 1.0 cc olive oil Controls: 1.0 cc olive oil	4, 3, 2 times at two months interval and once	Rat	Sprague-Dawley	13	150	150	300	60 M F	Life span
BT13	Subcutaneous injection	4.25 mg in 1.0 cc olive oil Controls: 1.0 cc olive oil	1 injection	Rat	Sprague-Dawley	21	70	80	150	75 M F	Life span

Table 13

BT Project on VC carcinogenicity. Exp. BT 11, 27 : plan

Route of administration: ingestion (stomach tube). Test animals: Sprague-Dawley rats

Purpose: evaluation of the effects of the route of administration on VC carcinogenicity

Experiment	Treatment			Animals							Duration of the experiment
							No.				
	Route	Dosese of VC	Duration	Species	Strain	(weeks)	M	F	Total	Per group	
BT11	Ingestion	50 mg, 16.65 mg, 3.33 mg/kg body weight in olive oil Controls: olive oil	5 times weekly 52 weeks	Rat	Sprague-Dawley	13	160	160	320	80 M F	Life span
BT27	Ingestion	1 mg, 0.3 mg, 0.03 mg/kg body weight in olive oil Controls: olive oil	5 times weekly, 52 weeks and 59 weeks (1)	Rat	Sprague-Dawley	10	300	300	600	150 M F	Life span

(1) For 10 animals of each of the 3 exposed and control groups the treatment was planned to last 104 weeks, but it had to be stopped because of animal intolerance.

Table 14

BT Project on VC carcinogenicity: test compound

Test compound: A) Supplier :	Montedison, Italy		
B) Purity :	Vinyl chloride	99.97%	
	H_2O	100	ppm
	acetic aldehyde	5	ppm
	acetilene	2	ppm
	allene	5	ppm
	butane	8	ppm
	1,3-butadiene	10	ppm
	chlorophene	10	ppm
	diacetylene	4	ppm
	vinyl acetylene	10	ppm
	propine	3	ppm
	methyl chloride	100	ppm

Table 15

BT Project on VC carcinogenicity: histopathology

Histopathological examination was performed on :

brain and cerebellum, Zymbal glands, interscapular brown fat, salivary glands, tongue, thymus, lungs, liver, kidneys, adrenals, spleen, pancreas, (esophagus) (1), stomach, various segments of intestine, bladder, uterus, gonads (tissues at the site of injection)(2), and any other organ with pathological lesions

(1) Only in the experiments in which VC was administered by injection.

(2) Only in the experiments in which VC was administered by injection (subcutaneous and intraperitoneal)

Table 16

Bt Project on VC carcinogenicity: tumours shown to be correlated to VC exposure, in the three tested animal species

Species	Mammary malignant tumours (mainly carcinomas)	Zymbal gland carcinomas	Nephroblastomas	Liver angiosarcomas, angiomas and fibroangiomas	Angiosarcomas, angiomas and fibroangiomas of other sites	Hepatomas	Encephalic neuroblastomas	Forestomach papillomas and acanthomas	Lung adenomas	Cutaneous epithelial tumours	Melanomas	Acustic duct epithelial tumours	Lymphomas and leukaemias
Rat	+	+	+	+	+	+	+	+	+	(+)			
Mouse	+			+	+	(+)		(+)	+	(+)			
Hamster				+	(+)			+		(+)	(+)	+	(+)

Table 17

BT Project. Exp. BT 1 : incidence of total malignant tumours in Sprague-Dawley rats, in relation to concentration of VC administered by inhalation, for 52 weeks

Experiment	Concentration (ppm)	Tumours/100 Animals Malignant tumours		
		M	F	Total
BT 1	10,000	80.0	83.3	81.7
	6,000	46.7	73.3	60.0
	2,500	53.3	73.3	63.3
	500	23.3	80.0	51.7
	250	23.3	36.7	30.0
BT 1	50	6.7	23.3	15.0
Control BT 1	0	-	26.7	13.3

Table 18

BI Project. Exp. BIII: exposure by ingestion (stomach tube) to VC in olive oil at 50.00, 16.65 and 3.33 mg/kg body weight, once daily, 4-5 days weekly, for 52 weeks.
Results after 136 weeks (end of the experiment).

Distribution of the different types of tumours

(first part)

Group No.	Dose	Animals (Sprague Dawley rats, 13 weeks old at start)			Animals with tumours																							
					Mammary tumours (b)			Zymbal gland carcinomas			Leukaemias			Nephroblastomas			Angiosarcomas						Angiomas and fibroangiomas					
																	Liver			Other sites			Liver			Other sites		
		Sex	No. at start	Corrected number (a)	Total No.	% (c)	Average latency time (weeks) (d)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)
I	50.00 mg/kg	M	40	40	1	2.5	81.0	1	2.5	82.0	1	2.5	83.0	1	2.5	76.0	8	20.0	83.1	0	-	-	1	2.5	108.0	1	2.5	73.0
		F	40	40	16	40.0	87.7	0	-	-	0	-	-	1	2.5	97.0	9	22.5	74.8	2	5.0	71.5	2	5.0	100.5	1	2.5	97.0
		M.F	80	80	17	21.2	87.3	1	1.2	82.0	1	1.2	83.0	2	2.5	86.5	17	21.2	78.7	2	2.5	71.5	3	3.7	102.7	2	2.5	85.0
II	16.65 mg/kg	M	40	40	0	-	-	1	2.5	116.0	0	-	-	2	5.0	88.5	4	10.0	64.0	0	-	-	0	-	-	0	-	-
		F	40	40	14	35.0	91.2	1(g)	2.5	54.0	1	2.5	69.0	1	2.5	75.0	6	15.0	89.5	0	-	-	0	-	-	0	-	-
		M.F	80	80	14	17.5	91.2	2	2.5	85.0	1	1.2	69.0	3	3.7	84.0	10	12.5	79.3	0	-	-	0	-	-	0	-	-
III	3.33 mg/kg	M	40	40	1	2.5	101.0	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-
		F	40	40	14	35.0	95.5	0	-	-	0	-	-	0	-	-	0	-	-	2	5.0	93.5	0	-	-	1	2.5	105.0
		M.F	80	80	15	18.7	95.9	0	-	-	0	-	-	0	-	-	0	-	-	2	2.5	93.5	0	-	-	1	1.2	105.0
IV	Olive oil	M	40	40	0	-	-	0	-	-	1	2.5	91.0	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-
		F	40	40	11	27.5	91.6	1	2.5	104.0	1	2.5	87.0	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-
	(Control)	M.F	80	80	11	13.7	91.6	1	1.2	104.0	2	2.5	89.0	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-
Total			320	320																								

(a) Alive animals at 2 weeks, when the first tumour (a forestomach acanthoma) was observed.
(b) Two or more tumours of the same and/or different types (fibroadenomas, carcinomas, sarcomas, carcinosarcomas) may be present in the same animal.
(c) The percentages are referred to the corrected number.
(d) Average age at the onset of the first mammary tumour per animal detected at the periodic examination or at autopsy.
(e) Average time from the start of the experiment to the detection (at the periodic examination or at autopsy).
(f) Several animals with two or more tumours.
(g) 1 with carcinomatous component.

Table 18

BT Project. Exp. BT11: exposure by ingestion (stomach tube) to VC in olive oil at 50.00, 16.65 and 3.33 mg/kg body weight, once daily, 4-5 days weekly, for 52 weeks.
Results after 136 weeks (end of the experiment).

Distribution of the different types of tumours

(second part)

Group No.	Dose	Animals with tumours																							
		Hepatomas			Forestomach epithelial tumours			Skin carcinomas			Subcutaneous sarcomas			Encephalic tumours					Others			Total (f)		
														Neuroblastomas			Other types								
		Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Total No.	Benign No.	Malignant No.	No.	% (c)	No. of different tumours / tumour bearing animals
I	50.00	0	-	-	2	5.0	34.0	1	2.5	84.0	0	-	-	0	-	-	0	-	5	3	2	17	42.5	1.3
	mg/kg	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-	1	2.5	4	4	0	25	62.5	1.4
		0	-	-	2	2.5	34.0	1	1.2	84.0	0	-	-	0	-	-	1	1.2	9	7	2	42	52.5	1.3
II	16.65	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-	1	2.5	1	0	1	9	22.5	1.0
	mg/kg	0	-	-	1	2.5	76.0	0	-	-	0	-	-	0	-	-	0	-	4	4	0	18	45.0	1.6
		0	-	-	1	1.2	76.0	0	-	-	0	-	-	0	-	-	1	1.2	5	4	1	27	33.7	1.4
III	3.33	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-	1	2.5	1	1	0	3	7.5	1.0
	mg/kg	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-	0	-	11	9	2	19	47.5	1.5
		0	-	-	0	-	-	0	-	-	0	-	-	0	-	-	1	1.2	12	10	2	22	27.5	1.4
IV	Olive	0	-	-	0	-	-	1	2.5	70.0	0	-	-	0	-	-	1	2.5	6	4	2	7	17.5	1.0
	oil	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-	0	-	6	6	0	17	42.5	1.1
	(Control)	0	-	-	0	-	-	1	1.2	70.0	0	-	-	0	-	-	1	1.2	12	10	2	24	30.0	1.1

Total

(a) Alive animals at 2 weeks, when the first tumour (a forestomach acanthoma) was observed.
(b) Two or more tumours of the same and/or different types (fibroadenomas, carcinomas, sarcomas, carcinosarcomas) may be present in the same animal.
(c) The percentages are referred to the corrected number.
(d) Average age at the onset of the first mammary tumour per animal detected at the periodic examination or at autopsy.
(e) Average time from the start of the experiment to the detection (at the periodic examination or at autopsy).
(f) Several animals with two or more tumours.

Table 19

BT Project. Exp. BT11 : exposure by ingestion (stomach tube) to VC in olive oil at 50.00, 16.65 and 3.33 mg/kg body weight, once daily, 4-5 days weekly, for 52 weeks.
Results after 136 weeks (end of the experiment).

Distribution of the different types of miscellaneous ("others") tumours

Group No.	Sex	Animals bearing other tumours				
		Benign		Malignant		Total
		No.	Distribution of histotypes	No.	Distribution of histotypes	
I	M	3	2 adrenal gland cortical adenomas 1 pheochromocytoma	2	1 carcinoma of the parotid gland 1 pulmonary adenocarcinoma	5
	F	4	2 cholangiomas 2 pheochromocytomas	0	-	4
II	M	0	-	1	1 pheochromoblastoma	1
	F	4	1 skin acanthoma 1 cholangioma 2 adrenal gland cortical adenomas	0	-	4
III	M	1	1 bladder papilloma	0	-	1
	F	9	1 subcutaneous lipoma 3 adrenal gland cortical adenomas 4 pheochromocytomas 1 polypus of the uterus	2	1 dermal fibrosarcoma 1 osteosarcoma	11
IV	M	4	4 pheochromocytomas	2	1 adrenal gland cortical adenocarcinoma 1 bladder carcinoma	6
	F	6	1 subcutaneous lipoma 1 auditory tract papilloma 2 adrenal gland cortical adenomas 2 pheochromocytomas	0	-	6

Table 20

BT Project. Exp. BT11: exposure by ingestion (stomach tube) to VC in olive oil at 50.00, 16.65 and 3.33 mg/kg body weight, once daily, 4-5 days weekly, for 52 weeks.
Results after 136 weeks (end of the experiment).

Incidence of total malignant tumours

Group No.	Dose	Animals (Sprague-Dawley rats, 12 weeks old at start)		Total malignant tumours	
		Sex	No. at start	No.	% (a)
I	50.00 mg/kg	M	40	14	35.0
		F	40	17	42.5
		M+F	80	31	38.7
II	16.65 mg/kg	M	40	9	22.5
		F	40	15	37.5
		M+F	80	24	30.0
III	3.33 mg/kg	M	40	2	5.0
		F	40	6	15.0
		M+F	80	8	10.0
IV	Olive oil (Control)	M	40	5	12.5
		F	40	6	15.0
		M+F	80	11	13.7
Total			320		

(a) The percentages are referred to the number at start.

Table 21

BI Project. Exp. BI27: exposure by ingestion (stomach tube) to VC in olive oil at 1.0, 0.3, 0.03 mg/kg body weight, once daily, 4-5 days weekly, for 59 weeks.
Results after 136 weeks (end of the experiment).

Distribution of the different types of tumours

(first part)

Group No.	Dose	Animals (Sprague Dawley rats, 10 weeks old at start)			Animals with tumours																							
					Mammary tumours (b)			Zymbal gland carcinomas			Leukaemias			Nephroblastomas			Angiosarcomas						Angiomas and fibroangiomas					
																	Liver			Other sites			Liver			Other sites		
		Sex	No. at start	Corrected number (a)	Total No.	% (c)	Average latency time (weeks) (d)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)
I	1.0 mg/kg	M	75	74	5	6.7	91.2	2	2.7	96.0	1	1.3	111.0	0	-	-	1	1.3	129.0	0	-	-	0	-	-	0	-	-
		F	75	75	39	52.0	83.4	3	4.0	103.0	5	6.7	89.0	0	-	-	2	2.7	96.5	1	1.3	91.0	0	-	-	0	-	-
		M+F	150	149	44	29.5	84.3	5	3.3	100.2	6	4.0	92.7	0	-	-	3	2.0	107.3	1	0.7	91.0	0	-	-	0	-	-
II	0.3 mg/kg	M	75	75	3	4.0	108.3	0	-	-	4	5.3	107.2	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-
		F	75	73	31	42.5	81.1	0	-	-	0	-	-	0	-	-	1	1.4	101.0	0	-	-	1	1.4	116.0	0	-	-
		M+F	150	148	34	23.0	83.5	0	-	-	4	2.7	107.2	0	-	-	1	0.7	101.0	0	-	-	1	0.7	116.0	0	-	-
III	0.03 mg/kg	M	75	75	1	1.3	138.0	0	-	-	3	4.0	92.0	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-
		F	75	75	42	56.0	78.6	0	-	-	1	1.3	129.0	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-
		M+F	150	150	43	28.7	80.0	0	-	-	4	2.7	102.2	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-
IV	Olive oil (Control)	M	75	75	2	2.7	75.0	0	-	-	4	5.3	59.7	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-
		F	75	75	35	46.7	84.8	1	1.3	90.0	3	4.0	96.0	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-
		M+F	150	150	37	24.7	84.3	1	0.7	90.0	7	4.7	75.3	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-
Total			600	597																								

(a) Alive animals at 12 weeks, when the first tumour (a mammary carcinoma) was observed.
(b) Two or more tumours of the same and/or different types (fibroadenomas, carcinomas, sarcomas, carcinosarcomas) may be present in the same animal.
(c) The percentages are referred to the corrected number.
(d) Average age at the onset of the first mammary tumour per animal detected at the periodic examination or at autopsy.
(e) Average time from the start of the experiment to the detection (at the periodic examination or at autopsy).
(f) Several animals with two or more tumours.

Table 21

BT Project. Exp. BT27: exposure by ingestion (stomach tube) to VC in olive oil at 1.0, 0.3, 0.03 mg/kg body weight, once daily, 4-5 days weekly, for 59 weeks.
Results after 136 weeks (end of the experiment).

Distribution of the different types of tumours

(second part)

Group No.	Dose	Animals with tumours																							
		Hepatomas			Forestomach epithelial tumours			Skin carcinomas			Subcutaneous sarcomas			Encephalic tumours					Other tumours				Total (f)		
														Neuroblastomas			Other sites							
		Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Average latency time (weeks) (e)	Total No.	% (c)	Total No.	Benign No.	Malignant No.	No.	% (c)	No. of different tumours/ tumour bearing animals
I	1.0	1	1.3	97.0	1	1.3	104.0	0	-	-	3	4.0	75.3	0	-	-	2	2.7	3	3	0	15	20.3	1.3
	mg/kg	0	-	-	2	2.7	88.5	0	-	-	0	-	-	0	-	-	1	1.3	12	9	3	53	70.7	1.2
		1	0.7	97.0	3	2.0	93.7	0	-	-	3	2.0	75.3	0	-	-	3	2.0	15	12	3	68	45.6	1.2
II	0.3	1	1.3	103.0	2	2.7	103.5	0	-	-	0	-	-	0	-	-	4	5.3	10	10	0	17	22.7	1.4
	mg/kg	0	-	-	0	-	-	1	1.4	62.0	0	-	-	0	-	-	2	2.7	3	0	3	35	47.9	1.1
		1	0.7	103.0	2	1.3	103.5	1	0.7	62.0	0	-	-	0	-	-	6	4.0	13	10	3	52	35.1	1.2
III	0.03	0	-	-	1	1.3	88.0	1	1.3	94.0	1	1.3	42.0	0	-	-	0	-	10	10	0	15	20.0	1.1
	mg/kg	0	-	-	1	1.3	89.0	0	-	-	0	-	-	0	-	-	2	2.7	8	5	3	46	61.3	1.2
		0	-	-	2	1.3	88.5	1	0.7	94.0	1	0.7	42.0	0	-	-	2	1.3	18	15	3	61	40.7	1.2
IV	Olive	0	-	-	2	2.7	85.0	0	-	-	0	-	-	0	-	-	2	2.7	3	3	0	13	17.3	1.0
	oil	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-	4	5.3	8	5	3	39	52.0	1.3
	(Control)	0	-	-	2	1.3	85.0	0	-	-	0	-	-	0	-	-	6	4.0	11	8	3	52	34.7	1.2

Total

(a) Alive animals at 12 weeks, when the first tumour (a mammary carcinoma) was observed.
(b) Two or more tumours of the same and/or different types (fibroadenomas, carcinomas, sarcomas, carcinosarcomas) may be present in the same animal.
(c) The percentages are referred to the corrected number.
(d) Average age at the onset of the first mammary tumour per animal detected at the periodic examination or at autopsy.
(e) Average time from the start of the experiment to the detection (at the periodic examination or at autopsy).
(f) Several animals with two or more tumours.

Table 22

BT Project. Exp. BT 27: exposure by ingestion (stomach tube) to VC in olive oil, at 1.0, 0.3, 0.03 mg/kg body weight, once daily, 4-5 days weekly, for 59 weeks.
Results after 136 weeks (end of the experiment)

Distribution of the different types of miscellaneous ("others") tumours

Group No.	Sex	Animals bearing other tumours				Total
		Benign		Malignant		
		No.	Distribution of histotypes	No.	Distribution of histotypes	
I	M	3	3 dermatofibromas	0	-	3
	F	9	1 dermatofibroma 1 Zymbal gland adenoma 2 cholangiomas 1 duodenal fibroma 1 caecum lipoma 1 pheochromocytoma 1 thecoma 1 odontoma	3	1 kidney fibrosarcoma 1 peritoneal fibrosarcoma 1 adenocarcinoma of the uterus	12
II	M	10	1 dermatofibroma 1 subcutaneous lipoma 1 adrenal gland cortical adenoma 7 pheochromocytomas	0	-	10
	F	0	-	3	1 pelvis carcinoma 1 adenocarcinoma of the uterus 1 leiomyosarcoma of the uterus	3
III	M	10	4 dermatofibromas 1 Zymbal gland adenoma 1 subcutaneous fibroma 1 subcutaneous lipoma 3 pheochromocytomas	0	-	10
	F	5	1 skin acanthoma 1 adrenal gland cortical adenoma 1 pheochromocytoma 1 fibromatous polypus of the uterus 1 fibroma of the uterus	3	1 fibrosarcoma of the uterus 1 leiomyosarcoma of the uterus 1 arrhenoblastoma	8
IV	M	3	1 adenoma of exocrine pancreas 2 pheochromocytomas	0	-	3
	F	5	1 glandular stomach polypus 1 cholangioma 1 adrenal gland cortical adenoma 2 pheochromocytomas	3	1 kidney adenocarcinoma 1 adenocarcinoma of the uterus 1 fibrosarcoma of the uterus	8

Table 23

BT Project. Exp. BT27: exposure by ingestion (stomach tube) to VC in olive oil at 1.0, 0.3 and 0.03 mg/kg body weight, once daily, 4-5 days weekly, for 59 weeks. Results after 136 weeks (end of the experiment).

Incidence of total malignant tumours

Group No.	Dose	Animals (Sprague-Dawley rats, 10 weeks old at start)		Total malignant tumours	
		Sex	No. at start	No.	% (a)
I	1.0 mg/kg	M	75	10	13.3
		F	75	27	36.0
		M+F	150	37	24.7
II	0.3 mg/kg	M	75	9	12.0
		F	75	11	14.7
		M+F	150	20	13.3
III	0.03 mg/kg	M	75	6	8.0
		F	75	20	26.7
		M+F	150	26	17.3
IV	Olive oil (control)	M	75	6	8.0
		F	75	18	24.0
		M+F	150	24	16.0
Total			600		

(a) The percentages are referred to the number at start.

Table 24

BT Project on VC carcinogenicity: tumours significantly in excess

(Fisher exact probability test : $p \leq 0.05$)

Total cancer bearing animals	M	30,000; 10,000; 6,000; 2,500; 500; 250; 200; 50 ppm.
		50 mg/kg b.w.
	F	30,000; 10,000; 6,000; 2,500; 500; 200; 150; 50 ppm.
		50 mg/kg b.w.
Mammary gland carcinoma	F	150; 50; 25, 10; 5 ppm.
Zymbal gland carcinoma	M	30,000; 10,000 ppm.
	F	30,000; 10,000 ppm.
Nephroblastoma	M	2,500; 200; 150; 100 ppm.
	F	500; 250 ppm.
Liver angiosarcoma	M	30,000; 2,500; 200 ppm.
		50 mg/kg b.w.
	F	30,000; 6,000; 2,500; 500; 200; 150; 50 ppm.
		50; 16.65 mg/kg b.w.
Neuroblastoma	F	10,000 ppm.
Forestomach papilloma and acanthoma	M	30,000 ppm.
	F	30,000 ppm.

Table 25

BT Project on VC carcinogenicity: tumours considered as VC correlated, at the lowest doses

at 25 ppm	: over 120 animals 5 liver angiosarcomas, 4 Zymbal gland carcinomas and 1 nephroblastoma.
at 10 ppm	: over 120 animals 1 liver angiosarcoma, 2 extrahepatic angiosarcomas and 2 Zymbal gland carcinomas.
at 1 mg/kg	: over 150 animals 3 liver angiosarcomas, 1 extrahepatic angiosarcoma, 1 hepatoma and 5 Zymbal gland carcinomas.
at 0.3 mg/kg	: over 150 animals 1 liver angiosarcoma and 1 hepatoma.

Table 26

Distribution by country of 119 cases of angiosarcoma of liver among workers exposed to VC

Country	No.of cases
United States	35
W Germany	26
France	18
Canada	10
United Kingdom	9
Sweden	5
Italy	5
Yugoslavia	4
Czechoslovakia	2
Japan	2
Belgium	2
Norway	1
All countries reporting cases	119

Table 27

The history of VC carcinogenicity

1)	1970	: Zymbal gland carcinomas were reported in rats exposed to 30,000 ppm of VC, by inhalation (Viola et al., 1971)
2)	1970	: An increase in atypias in respiratory cells was observed among workers heavily exposed to VC (Maltoni et al., 1974 a)
3)	1971 (July)	: A vast project of long-term carcinogenicity bioassays on VC was started in Bentivoglio, near Bologna, Italy (BT Project)
4)	1972 (August)	: Zymbal gland carcinomas, nephroblastomas and liver angiosarcomas were observed in rats exposed to VC by inhalation (Maltoni, BT Project)
5)	1973 (April)	: The first data of the BT Project were released to the Scientific community: the oncogenic effect was observed up to 250 ppm (Maltoni, 1974 a, b)
6)	1973	: Splenomegalic liver disease was found among polyvinyl chloride production workers (Marsteller et al., 1973)
7)	1973 (December)	: For the first time a case of liver angiosarcoma in a worker of polyvinyl chloride production was correlated to VC exposure (Creech and Johnson, 1974)
8)	1974 (February)	: On the basis of the BT Project data indicating a carcinogenic effect at 250 ppm, OSHA proposed a TLV of 50 ppm (Maltoni, 1974 b)
9)	1974 (February)	: The BT Project data showed that VC is a multipotential carcinogen, producing a variety of tumours, in different animal species (Maltoni, 1974 b, c)
10)	1974	: The BT Project data indicated a carcinogenic effect at 50 ppm. OSHA proposed new stricter rules (Maltoni, 1974 c; Maltoni and Lefemine, 1975)
11)	1974	: Early epidemiological observations (paralleling the experimental information) indicated an increase in tumours other than liver angiosarcomas (of brain, lung, hepatocytes, haemolymphoreticular tissues) among workers of VC-PVC industries (Wagoner, 1974)
12)	1974-75	: BT Project data showed that VC had carcinogenic effects in rats also when given by ingestion (Maltoni et al., 1975 a, b)
13)	1976	: In rats of the BT Project exposed to VC by inhalation, angiosarcomas were observed down to the level of 25 ppm, and Zymbal gland carcinomas down to the level of 10 ppm (Maltoni, 1977 a)