

BIO-MEDICAL RESEARCH
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THE VALUE OF PROGNOSTIC EXERCISES IN CARDIOVASCULAR DISEASES. AN EXPERIMENTAL STUDY — Rate, Indication, Interpretation	21 22 23 24

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Brief Summary

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The Value of Predictive Experimental Environmental Carcinogeneses

An Example: Vinyl Chloride

BY CESARE MALTONI

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The vinyl chloride story demonstrates the need for experimental carcinogenicity testing of chemical compounds before they are released into the occupational and general environment.

It is increasingly demonstrated and accepted that the high and rising incidence of tumors, especially in particular sites (lung, urinary tract, hemopoietic tissues), is due to the extensive and growing diffusion of oncogenic agents in the environment.

Furthermore it is assumed that 80 to 90 percent of tumors depend on causes which are, or may be identified as being, part of the human environment. Recognition of such causes and protection from their effects could significantly reduce tumor morbidity and mortality.

This increasing diffusion of environmental oncogenic agents is a phenomenon particularly correlated to the growth of industrialization, and especially to those industries producing and manufacturing new synthetic compounds. In modern times, from 100 000 to 200 000 new chemical compounds are produced annually, and we know very little about their effects on man.

There is a strict correlation between occupational and general environmental carcinogeneses. Potential carcinogenic agents spread in fact throughout the general environment from the factories where they are produced, thus rapidly creating an ecological problem. Hence, results of studies in the field of occupational oncogenesis, directed towards identifying oncogenic industrial agents and assessing protective measures for workers, can be extrapolated easily to general environmental oncogenesis.

Environmental and occupational carcinogeneses are, therefore, socially important. As regards occupational carcinogenesis, it is one of the most interesting, tragic and difficult

fields in oncology: it is *interesting* from a scientific standpoint because it represents, dramatically, an experiment on human beings which has taught us much about the natural history of tumors; *tragic* because work, which is, *per se*, a natural necessity of life, *should not* cause cancer, and *difficult* because the care of workers' health often conflicts with the productive goals of industry and with major economic and political interests.

NEED FOR PREDICTIVE CARCINOGENICITY BIOASSAYS

Most of the oncogenic occupational and environmental agents have been identified when the incidence of a particular type of tumor in an exposed population has been outstanding, or on the basis of retrospective epidemiological studies.

Progress in these areas of oncology should facilitate systematic experimental carcinogenicity testing of agents which are, or will be, released in the general and occupational environment. These testing should be carried out before the exposure of humans to potentially oncogenic agents takes place (since the specific effects on tissues produced by carcinogens are irreversible) and before economical, political and social interests are well established (as then they can not easily be changed).

Carcinogenicity experimental bioassays are surprisingly few as compared with the need. This is due to several factors: scepticism concerning the validity of testing, the vast amount

Bioassays in Occupational and

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of agents to be tested, complications in performing elaborate tests, lack of experimental units and conflict of responsibilities.

Let us briefly and critically review these points:

Scepticism. Too frequently in the past, environmental and occupational agents have been tested improperly so that the results could not be extrapolated to man. Consequently, experimental testing has often been considered obsolete for predicting carcinogenic risks. In our opinion, one should not be sceptical of the validity of carcinogenicity bioassays, but rather critically evaluate the methods of testing.

Vast amount of agents. Since this is a reality, one must establish priorities for the products which are, or will be, most widely diffused.

Complications in performing elaborate testings. The more experimental tests on animals reproduce the conditions of human exposure, the more relevant they are to man. Agents to be examined should follow a pattern of tests which progress in degree of preciseness and scrutiny, so as to filter out and expose the more dangerous compounds.

Lack of experimental units and conflict of responsibilities. The number of oncological units throughout the world performing carcinogenicity bioassays is indeed low (if one does not include those centers or agencies whose activity is devoted mainly to promoting public relations in this field) and are not sufficiently coordinated. Moreover it is often difficult to assess (because of the large number and lack of correlation between governmental and intergovernmental agencies) who is responsible for promoting such studies, verifying the results and undertaking proper protective measures. A permanent intergovernmental commission, together with representatives from interested parties, should: 1) plan the programs and priorities, 2) promote at an international level an adequate and integrative network of experimental units, and 3) critically evaluate the results and decide on proper preventive programs.

In sharp contrast to the insufficient attention given experimental carcinogenicity bioassays for predicting potential risks, there are numerous projects which study the carcinogenic effect on experimental animals and the metabolic patterns of agents which are already known to be carcinogenic for man. These studies, of course, may be of some interest for basic oncology, but they have little bearing on the prevention of occupational and environmental tumors.

Furthermore, medical controls have been given great emphasis. In our opinion, the value of medical examinations is mainly to determine the risk; that is, they may provide epidemiological data. In fact, as collective information and our own experience have shown, the carcinogens exert their effects on a broad range of organs in exposed humans and affect widely the target organs, and the tumors which arise are

potentially multicentric. Consequently very little can be done after the tumors have arisen.

The major value of experimental testing in the prevention of occupational and environmental oncogeneses is demonstrated clearly by the story of vinyl chloride carcinogenicity.

VINYL CHLORIDE CARCINOGENESIS

Vinyl Chloride (VC) has been produced in many countries for more than 30 years. It is the constituent of polyvinyl chloride (PVC) which today is the plastic industrial material most often used and diffused throughout the world. Moreover, it is used as a copolymer in Saran and other plastics, as a chemical intermediate, as a solvent, and as a propellant. In the past, for only a short period, it was also used as an anaesthetic. VC at present is produced at a rate of almost 12 million tons per year.

The following population groups may be exposed to VC: 1) workers engaged in the production of PVC and VC, and in the use of VC for other industrial purposes; 2) workers manufacturing PVC; 3) residents in areas neighboring factories producing PVC and VC; and to a much lesser extent 4) people consuming products containing VC, as some propellant sprays; 5) people having contact with resins made with VC and with materials containing these resins; and 6) populations consuming food contained in plastic made by VC.

Valuable bioassays on the long term effects of VC were not available until 1970. This situation reflects the scarce consideration which has been given until now to experimental bioassays in predicting the oncogenic effects of environmental and occupational agents on man.

At the end of 1970 we planned a project of correlated investigations to clarify the type and degree of carcinogenic risk from VC.

This project included a series of experiments, which were started in sequence. They were designed to study the effects of VC, administered through different routes (inhalation, ingestion, peritoneal and subcutaneous injection), at different concentrations (by inhalation: 30 000, 10 000, 6000, 2500, 500, 250, 200, 150, 100, 50, 25, 10, 5, 1 ppm), for varying periods of time (by inhalation: from 52 weeks to 1 week), by continuous or intermittent treatment, on animals of different species (rats, mice, hamsters), strains (Sprague-Dawley and Wistar rats), sex and age (adults, newborn, embryos).

The planning of the program and the preparation of suitable experimental conditions, particularly the building of an apparatus for inhalatory exposure, took until May 1971. In July 1971 we started experimenting. The exposure by inhalation was generally performed 4 hours daily, five days per week.

The chambers of exposure, basically built of stainless steel and glass, have been designed to deliver concentrations of gaseous agents varying from 30 000 ppm to 1 ppm of VC. The VC concentration in the chambers is controlled by gas chrom-

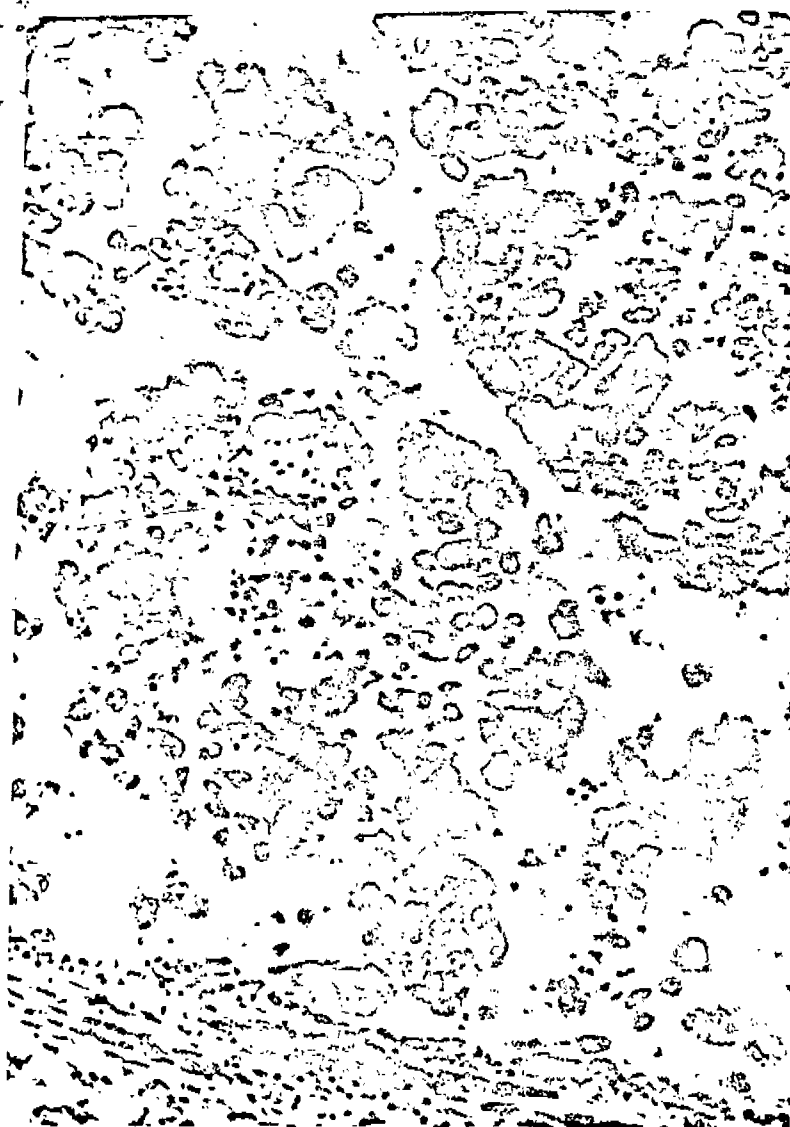


Figure 1. Liver angiosarcoma in a rat treated with VC. H.-E. X 125.



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Figure 2. Liver angiosarcoma in a worker exposed to VC. H.-E. X 125.

atography and now we simultaneously may treat 2500 rodents.

Fifteen experiments (BT1—15) were started. Some of them were programmed at the beginning, and others were started after results were obtained from the initial experiments.

All the animals are kept under observation until spontaneous death. The animals are controlled weekly and weighed every two weeks during the treatment period and monthly after treatment is completed. All detectable gross pathological changes are recorded during the control. The animals when moribund are isolated in order to avoid cannibalism.

A complete autopsy is made on each animal. Histological examinations are performed on Zymbal glands, interscapular brown fat, salivary glands, tongue, lungs, liver, kidneys, spleen, stomach, different segments of the intestine, bladder, brain, bones of the legs and feet and any other organ with pathological lesions.

The current results up to September 10 of several experiments (BT 1, 3, 7, 5, 4, 8) are shown in Tables 1—6. Among 60 Sprague-Dawley rats exposed by inhalation to 30 000 ppm of VC for 52 weeks (BT6) in the same way as the animals of experiment BT1, within 61 weeks from the beginning of the experiment, Zymbal gland carcinomas have been found in 30

animals and liver angiosarcomas in 13 animals. For the latter experiments, data are not yet available. Different types of tumors may be present in the same animal.

Zymbal gland carcinomas (in rats) may be bilateral. Histologically they frequently reproduce, to a certain extent, the structure of the normal Zymbal gland, but often they present squamous, glandular, solid, anaplastic and polymorphous patterns.

Nephroblastomas (in rats) are often bilateral. Their histological picture reminds us of an embryonal kidney. Hyperplasia of nephroblastema-like tissue is often observed in the kidney of treated rats, with or without nephroblastoma.

Angiosarcomas and angiomas (in rats, mice, hamsters) may be found at more than one site in the same animal. In the liver they are often polycentric. Hepatic (Figure 1) and extrahepatic angiosarcomas are more or less differentiated.

Blood vessel ectasias, endothelial hyperplasia, associated or not associated with cellular atypias, are often observed in the liver and in other organs and tissues in treated animals, with or without local or distant angiosarcomas or angiomas. Therefore, the effect of VC on blood vessels and endothelia should be considered systematic.

Treatment (a)	Animals (Sprague-Dawley rats)		Zymbal gland carcinomas (c)			Nephroblastomas (e)			Animals with tumors										Total (h)
									Angiosarcomas			Sub- cutane- ous angio- mas	Skin carci- nomas	Hepa- tomas	Brain neuro- blastoma- s	Other type and/or site (g)			
	Liver (f)			Other sites	No.	No.	No.	No.	No.	No.									
	Total	Cor- rected number (b)	No.	% (d)	Average latency time (weeks)	No.	% (d)	Average latency time (weeks)	No.	% (d)	Average latency time (weeks)	No.	No.	No.	No.	No.	No.	No.	
VC 10000 ppm	69	61	16	26	50	5	8	59	9	15	64	3 (i)	4	3	1	7	7 (o)	38	
VC 6000 ppm	72	60	7	12	62	4	7	65	13	22	70	3 (j)	3	1	1	3	8 (p)	31	
VC 2500 ppm	74	59	2	3	33	6	10	74	13	22	78	3 (k)	3	1	2	5	4 (q)	32	
VC 500 ppm	67	59	4	7	79	4	7	83	7	12	81	2 (l)	1	1	3	—	4 (r)	22	
VC 250 ppm	67	59	—	—	—	6	10	80	4	7	79	2 (m)	—	—	—	—	3 (s)	16	
VC 50 ppm	61	59	—	—	—	1	2	135	1	2	135	1 (n)	1	1	—	—	9 (t)	10	
No treatment	68	58	—	—	—	—	—	—	—	—	—	—	—	—	—	—	10 (u)	6	
Total	577	484	29	—	—	26	—	—	47	—	—	14	12	11	7	15	45	155	

- (a) The animals were treated by inhalation for 4 hours daily, 5 days weekly, for 52 weeks.
 (b) Animals alive after 28 weeks, when the first tumor (a Zymbal gland carcinoma) was observed. The percentages are referred to the corrected number.
 (c) Metastases to lung.
 (d) Percentage of corrected number.
 (e) Metastases to liver, lung, spleen and brain.
 (f) Metastases to lung.
 (g) Several cases of breast fibroadenomas, adrenal and pituitary tumors (generally adenomas) have not been considered, since their distribution in the different groups does not vary.
 (h) Several animals with 2 or more tumors.
 (i) 1 angiosarcoma of the lips; 1 angiosarcoma of the nose; 1 intra-abdominal angiosarcoma (next to liver).
 (j) 1 angiosarcoma in subcutaneous fibrosing angioma; 1 ossifying parauricular angiosarcoma; 1 intra-abdominal angiosarcoma (next to liver).
 (k) 2 intra-abdominal angiosarcomas (1 next to spleen and 1 next to ovary); 1 ossifying angiosarcoma of the neck.

- (l) 1 pulmonary angiosarcoma; 1 angiosarcoma of the uterus.
 (m) 1 intra-abdominal angiosarcoma (next to spleen); 1 intrathoracic ossifying angiosarcoma.
 (n) 1 intra-abdominal diffused angiosarcoma.
 (o) 2 Zymbal gland adenomas; 3 mammary carcinomas; 1 neurilemmoma; 1 ovarian cystadenocarcinoma.
 (p) 4 Zymbal gland adenomas; 1 salivary gland adenocarcinoma; 2 hepatic and 1 peritoneal angiomas.
 (q) 1 Zymbal gland adenoma; 1 mammary carcinoma; 2 ependymomas.
 (r) 1 mammary carcinoma; 2 lymphomas; 1 pulmonary fibrosarcoma.
 (s) 1 Zymbal gland adenoma; 1 mammary carcinoma; 1 lymphoma.
 (t) 3 Zymbal gland adenomas; 2 mammary carcinomas; 1 subcutaneous angiosarcoma; 3 uterine adenocarcinomas (1 with sarcomatous component).
 (u) 1 invasive acanthoma of Zymbal gland; 1 subcutaneous fibrosarcoma; 2 peritoneal fibroangiomas, 2 uterine adenocarcinomas (1 with sarcomatous component); 1 uterine leiomyosarcoma; 1 ovarian fibrosarcoma; 1 pulmonary rhabdomyosarcoma; 1 lymphoma.

Table 2. Experiment BT3: Results after 86 weeks

Treatment (a)	Number of animals (Sprague-Dawley rats)		Number of animals with tumors (b)						Total (d)
	Total	Survivors	Zymbal gland carcinomas	Nephroblastomas	Angiosarcomas		Brain neuroblastomas	Other type and/or site (c)	
VC 10000 ppm	60	9	6 (16)	— (5)	— (9)	1 (e) (3)	6 (7)	3 (g) (15)	15 (40)
VC 6000 ppm	60	16	4 (7)	— (4)	— (11)	— (3)	2 (3)	7 (h) (9)	10 (27)
VC 2500 ppm	60	33	1 (2)	2 (4)	— (9)	— (3)	2 (2)	— (7)	5 (23)
VC 500 ppm	60	37	— (2)	— (2)	— (3)	— (2)	—	2 (i) (7)	2 (13)
VC 250 ppm	60	15	—	1 (4)	— (2)	— (1)	—	2 (j) (5)	3 (9)
VC 50 ppm	60	18	—	—	—	1 (f)	—	— (3)	1 (3)
No treatment	190	128	—	—	—	—	—	3 (k) (3)	2 (2)
Total	550	256	11 (27)	3 (19)	— (31)	2 (12)	10 (12)	17 (49)	38 (117)

- (a) The animals were treated by inhalation 4 hours daily, 5 hours weekly, for 17 weeks.
 (b) Between brackets are recorded the tumors found in experiment BT1 after 86 weeks.
 (c) Several cases of breast fibroadenomas, adrenal and pituitary tumors (generally adenomas) have not been considered, since their distribution in the different groups does not vary.
 (d) Several animals with 2 or more tumors.
 (e) 1 subcutaneous angiosarcoma.

- (f) 1 orbital angiosarcoma
 (g) 1 parauricular fibrosarcoma; 1 nasal papilloma; 1 renal adenoma.
 (h) 1 Zymbal gland fibroangioma; 1 subcutaneous angiosarcoma; 1 mammary carcinoma; 1 forestomach papilloma; 1 cranial osteoma.
 (i) 2 lymphomas.
 (j) 1 Zymbal gland adenoma; 1 retrobulbar fibroma.
 (k) 1 Zymbal gland adenoma; 2 lymphomas.

Table 3. Experiment BT7: Results after 61 weeks

Treatment (a)	Number of animals (Wistar rats)		Number of animals with tumors (b)						Total
	Total	Survivors	Zymbal gland carcinomas	Nephroblastomas	Angiosarcomas		Brain neuroblastomas	Other type and/or site	
VC 10000 ppm	30	8	— (7)	1 (3)	2 (3)	— (1)	1 (2)	2 (c) (7)	5 (18)
VC 6000 ppm	30	13	— (1)	— (1)	— (2)	— (1)	— (1)	— (1)	— (6)
VC 2500 ppm	30	8	— (1)	— (1)	— (1)	— (2)	—	— (1)	— (5)
VC 500 ppm	30	16	— (1)	—	—	—	—	—	1 (1)
VC 250 ppm	30	16	—	—	—	—	—	1 (d)	1
VC 50 ppm	30	22	—	—	—	—	—	—	—
No treatment	40	34	—	—	—	—	—	—	—
Total	220	117	— (10)	1 (5)	3 (6)	— (4)	1 (3)	3 (9)	7 (30)

- (a) The animals were treated by inhalation for 4 hours daily, 5 days weekly, for 52 weeks.
 (b) Between brackets are recorded the tumors found in male Sprague-Dawley rats of the experiment BT1, after 71 weeks.

- (c) 2 Zymbal gland adenomas.
 (d) 1 angioma of the caecum.

Table 4. Experiment BT3: Results after 30 weeks

Treatment (a)	Number of animals (Sprague-Dawley rats)		Number of animals with tumors					
	Total	Survivors	Zymbal gland carcinomas	Nephro- blastomas	Angiosarcomas		Other type and/or site	Total
					Liver	Other sites		
VC 10000 ppm Breeders	30	8	—	—	—	—	—	—
VC 6000 ppm Breeders	30	2	—	—	—	—	—	—
VC 10000 ppm Offspring	54	31	1	—	—	1 (b)	—	2
VC 6000 ppm Offspring	32	15	—	—	—	1 (c)	—	1
Total	146	56	1	—	—	2	—	3

(a) The breeders were treated by inhalation for 4 hours daily, from the 12th to the 18th day of pregnancy.

(b) Subcutaneous angiosarcoma on a 24-week-old male.
(c) Subcutaneous angiosarcoma on a 22-week-old female.

Table 5. Experiment BT4: Results after 61 weeks

Treatment (a)	Animals (Swiss mice)												Animals with tumors									
	Total			Corrected number (b)			Survivors			Pulmonary tumors (c)			Mammary carcinomas (d)			Liver angio-sarcomas	Vascular tumors of other type and/or site	Epithelial tumors of the skin	Other type and/or site	Total (e)		
																No.	No.	No.	No.	No.		
	♂	♀	♂	♀	♂	♀	♂	♀	♂	No.	%	Average latency time (weeks)	No.	%	Average latency time (weeks)	No.	No.	No.	No.	No.		
VC 10000 ppm	30	30	60	22	28	50	—	—	—	35	70	36	13	47	31	8	9 (f)	3 (l)	2 (p)	36		
VC 6000 ppm	30	30	60	26	28	54	—	—	—	38	70	38	8	28	33	5	9 (g)	6 (m)	4 (q)	39		
VC 2500 ppm	30	30	60	23	30	53	—	—	—	30	57	43	9	30	35	11	12 (h)	3 (n)	2 (r)	31		
VC 500 ppm	30	30	60	29	29	58	—	2	2	38	66	41	7	24	37	11	16 (i)	1 (o)	1 (s)	42		
VC 250 ppm	30	30	60	29	29	58	3	1	4	31	53	42	11	32	39	11	14 (j)	—	3 (t)	38		
VC 50 ppm	30	30	60	27	30	57	1	9	10	1	2	56	10	33	37	1	11 (k)	—	1 (u)	16		
No treatment	80	70	150	74	67	141	24	31	55	4	3	53	—	—	—	—	—	—	1 (v)	5		
Total	260	250	510	230	241	471	28	46	74	177	—	—	58	—	—	47	71	13	14	207		

(a) The animals were treated by inhalation for 4 hours daily, 5 days weekly, for 30 weeks.

(b) Animals alive after 16 weeks, when the first tumor (a mammary carcinoma) was observed. The percentages are referred to the corrected number.

(c) Adenomas, some of which undergoing malignant transformation.

(d) In females.

(e) Several cases with 2 or more tumors.

(f) 4 liver fibroangiomas; 3 subcutaneous angiomas, 1 heart fibroangioma; 1 ossifying interscapular angioma.

(g) 4 liver angiomas; 2 liver fibroangiomas; 1 subcutaneous angiosarcoma; 1 renal fibroangioma, 1 thymic angioma.

(h) 3 liver angiomas; 3 subcutaneous angiosarcomas; 1 subcutaneous angioma; 2 intra-abdominal angiosarcomas; 2 renal angiosarcomas; 1 pulmonary angioma.

(i) 1 liver angioma, 3 liver fibroangiomas; 2 subcutaneous angiosarcomas; 1 subcutaneous angioma; 1 subcutaneous fibroangioma; 1 intra-abdominal fibroangioma; 3 intra-abdominal angiosarcomas; 1 angioma of the caecum; 1 renal angiosarcoma; 1 pulmonary fibroangioma; 1 testicular fibroangioma.

(j) 5 liver angiomas; 5 liver fibroangiomas; 2 intra-abdominal angiosarcomas, 1 pulmonary angioma; 1 scrotal angioma.

(k) 2 liver angiomas; 2 liver fibroangiomas, 1 subcutaneous angiosarcoma, 2 subcutaneous angiomas; 1 subcutaneous fibroangioma; 1 intra-abdominal angioma; 1 intrathoracic fibroangioma, 1 angioma of the inter-scapular fat pad

(l) 2 squamous carcinomas; 1 invasive acanthoma.

(m) 5 squamous carcinomas; 1 acanthoma.

(n) 1 squamous carcinoma; 2 acanthomas.

(o) 1 acanthoma.

(p) 1 Zymbal gland adenoma; 1 forestomach papilloma

(q) 1 lymphoma; 1 subcutaneous leiomyosarcoma, 1 forestomach papilloma.

(r) 1 Harderian gland adenoma.

(s) 1 forestomach papilloma; 1 parotid gland mixed tumor.

(t) 1 Zymbal gland adenoma.

(u) 1 Zymbal gland adenoma; 1 lymphoma; 1 Leydig cell tumor.

(v) 1 parotid gland adenomcarcinoma.

(w) 1 lymphoma.

Table 6. Experiment BT8: Results after 48 weeks

Treatment (a)	Number of animals (Golden hamsters)		Number of animals with tumors						
	Total	Survivors	Liver angio-sarcomas	Skin trichoepitheliomas (b)	Melanomas	Lymphomas	Forestomach papillomas and acanthomas	Other type and/or site	Total (c)
VC 10000 ppm	35	9	—	3	—	—	—	—	3
VC 6000 ppm	32	8	—	2	1	1	3	1 (d)	5
VC 2500 ppm	33	11	—	1	—	—	4	—	4
VC 500 ppm	33	13	1	1	—	1	1	1 (e)	4
VC 250 ppm	32	8	—	1	—	1	—	—	2
VC 50 ppm	33	11	—	3	1	1	—	—	5
No treatment	70	35	—	2	—	—	—	—	2
Total	268	95	1	13	2	4	8	2	25

(a) The animals were treated by inhalation for 4 hours daily, 5 days weekly, for 30 weeks.

(b) Several cases with acanthosis and some undergoing malignant transformation.

(c) Several animals with 2 or more tumors.

(d) 1 hepatocarcinoma.

(e) 1 subcutaneous angioma.

Table 7. Tumors presently correlated to VC exposure (by inhalation) on experimental rodents and man.

Species	TUMORS									
	Angio-sarcomas of liver	Tumors of brain	Tumors of lung	Lymphomas and leukemias	Angiosarcomas and angiomias of other sites	Nephro-blastomas	Sebaceous carcinomas	Squamous tumors of epidermis	Mammary carcinomas	Hepa-tomas
Rat	+	+	+	+	+	+	+	+	(+)	+
Mouse	+	+	+	+	+	+	+	+	+	+
Hamster	+	+	+	+	(+)	+	+	+	+	+
Man	+	(-)	(+)	(+)	+	+	+	+	+	+

Angioblastic proliferation, angiomas and angiosarcomas in the liver and in other sites may or may not be associated with fibroplasia. From the histological observations, the sequence of local changes in the genesis of malignant vascular tumors appears to be as follows: endothelial hyperplasia, angiomas, atypias of endothelial cells in hyperplasia (dysplasia) and angiosarcomas.

Fibro-angioblastic proliferation undergoing fibrosis is frequently observed in the spleen of the treated rats and mice.

Skin carcinomas in treated rats appear frequently to arise from sebaceous glands, of which they may reproduce to some extent the morphological characteristics.

Hepatomas observed in treated rats are usually well differentiated. Metastases have been observed in the lung.

Brain neuroblastomas (in rats) are very similar to the human medulloblastomas.

Lung adenomas (in mice) are usually multicentric; their number is higher in animals treated with heavier doses. Many of these tumors appear to undergo early malignant transformation.

Mammary carcinomas (in mice) may be solitary or multiple. They are usually well differentiated adenocarcinomas, with monomorphous or polymorphous arrangement. The most distinct feature of these tumors is the frequency with which they present areas of squamous metaplasia.

Several of the tumors produced by VC are quite rare or exceptional. To our knowledge liver angiosarcomas, nephroblastomas and neuroblastomas have never been described as spontaneously occurring in rats. Liver and extrahepatic angiosarcomas have been induced only in a few instances in experimental rodents (rats, hamsters and mice) [for references see Maltoni and Lefemine (1)]. As far as we know, this is the first time in which nephroblastomas and neuroblastomas have been experimentally reproduced.

SUMMARY OF FINDINGS

In conclusion we found that:

1. Under our experimental conditions, VC produced tumors in the three animals species studied: rats, mice and hamsters.
2. The range of induced tumors varies to some extent from species to species. When given by inhalation VC produced: in rats, Zymbal gland carcinomas, nephroblastomas, angiosarcomas and angiomas of the liver and other sites, skin carcinomas, hepatomas and brain neuroblastomas; in mice, lung adenomas, mammary carcinomas of a peculiar type, angiosarcomas and angiomas of the liver and other sites, skin epithelial tumors; in hamsters, liver angiosarcomas and, as early evidence seems to suggest, skin trichoeplitheliomas, lymphomas and forestomach papillomas and acanthomas. Incidentally, liver angiosarcomas have been observed in all three animal species.
3. In the BT1 and BT4 experiments, VC shows a cancerogenic effect at 50 ppm.
4. From the BT1 experiment (the only one completed) a dose-response relationship clearly emerges, as far as angiosarcomas and nephroblastomas are concerned, in the lower dose ranges: *ie* from 500 ppm to 50 ppm for angiosarcomas, and from 250 ppm to 50 ppm for nephroblastomas.
5. A comparison of the results available at the present moment in rats exposed for 52 weeks and 17 weeks (BT1 and BT3 experiments) shows that the neoplastic response, particularly as far as angiosarcomas and nephroblastomas are concerned, is affected by the length of exposure to VC.
6. The comparison of the results obtained in rats of two different strains, *ie* Sprague-Dawley (BT1) and Wistar (BT7), at the present moment, seems to suggest that the strain factor considerably affects the neoplastic response.
7. The onset of two subcutaneous angiosarcomas and of one Zymbal gland carcinoma in the offspring of breeders exposed during pregnancy for 7 days, appears to indicate a transplacental effect of VC.

Our data have been periodically transmitted to the European companies which have supported our research, and are available to all interested parties.

Before the end of 1972, a short time after it was known that VC was inducing in rats not only Zymbal gland tumors, but also nephroblastomas and liver angiosarcomas, these results were also made known to the US Manufacturing Chemists Association (MCA). This information promoted the clinical observa-

tions which in December 1973, for the first time, identified a liver angiosarcoma—in a worker of a US factory producing VC-PVC—as occupational. Since then epidemiological investigations have led to the discovery of nearly 30 liver angiosarcomas (Figure 2) among workers of VC-PVC industries in the USA and several European countries. Most of these tumors arose before 1973 (the first known case dates from 1961), but in absence of experimental data, they were not linked to the occupational exposure, and as a matter of fact, they were often not properly diagnosed.

VC has caused in one or more of the three animal species used in our experiments, all types of tumors, which at present, on the basis of available epidemiological evidence, are correlated to occupational exposure, *ie* liver angiosarcomas, brain and lung tumors, lymphomas and leukemias (Table 7).

CONCLUSIONS

It is our hope that the story of VC carcinogenicity may serve as a convincing example to urgently promote experimental bioassays for all new industrial compounds, and for those compounds which are already produced and widespread, but whose effect we still ignore.

References and Notes:

1. C. Maltoni, G. Lefemine, *Environmental Research*, 7, 387 (1974).

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