ETHYL CORPORATION
TOXICOLOGY AND INDUSTRIAL HYGIENE DEPARTMENT
ETHYL TOWER, 451 FLORIDA
BATON ROUGE, LOUISIANA 70801
504/388-7858

CMA / Vinyl Chloride

July 16, 1979

T.R. Torkelson
1603 Building
Dow Chemical, USA
Midland, Michigan 48640

Dear Ted:

Enclosed is a copy of a research proposal from the University of Tennessee, Materials Science Toxicology Laboratories, for studying pulmonary effects by PVC dust.

This proposal is a result of our initial conversations concerning the potential hazards associated with PVC dust exposure in the workplace.

Dr. Autian has considerable expertise in the area of plastic toxicology studies and is quite interested in pursuing the PVC dust problem.

I would appreciate receiving your comments and those of the Vinyl Chloride Research Coordinators - CMA regarding this proposal.

Thank you for your assistance in forwarding copies to the coordinators as discussed during our telephone conversation.

Best regards,

Sincerely,

Theodore J. Benya, Ph.D.
Toxicologist

TJB:sbb
Attach.
cc: G.L. Ter Haar
J. Autian

SCC
1-0619

Materials Science Toxicology Laboratories

COLLEGE OF DENTISTRY & COLLEGE OF PHARMACY

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MEMPHIS, TENNESSEE 38163

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June 13, 1979

Dr. Theodore J. Benya, Toxicologist
Ethyl Corporation
Toxicology and Industrial Hygiene Department
Ethyl Tower, 451 Florida
Baton Rouge, Louisiana 70801

Dear Ted:

I am a little late in sending you the informal proposal developed by Dr. W. H. Lawrence and myself, and I hope this has not inconvenienced you. Please review what we have said and then let us know if it can be developed into a full-fledged proposal. I will be out-of-town for the next two weeks, and thus you may wish to talk to Dr. Homer Lawrence (901: 528-6068) if questions arise.

Hoping to hear from you soon.

Sincerely,

John Autian, Ph. D., Director

cc Dr. W. H. Lawrence

JA/rw

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TO: Dr. Theodore J. Benya, Toxicologist
Ethyl Corporation

FROM: Drs. John Autian and W.H. Lawrence
Materials Science Toxicology Laboratories

DATE: June 12, 1979

SUBJECT: Proposed Carcinogenic Study of PVC Dust

PROPOSAL FOR A FEASIBILITY STUDY TO EXAMINE THE POTENTIAL CARCINOGENICITY OF PVC DUST

Introduction

Because of the possible relationship between exposure to PVC dust and lung disorders, it became desirable to initiate a short-term feasibility study to assess the possibility that PVC dust might be implicated in pulmonary tumorgenesis. The latent period for such tumors, if induced by PVC dust, is unknown but tumor induction often is not observed until after a considerable lapse of time.

This proposal is designed as a six-months study, but sufficient animals will be treated to provide for a number of animals remaining after completion of the six-month design to permit extending the study, without the delay of starting over from the beginning, for a longer period of time if results from the

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six-months study would suggest it might be fruitful. These 'extra' animals will be held until the histological evaluations of the six-month tissues have been completed; at this time a decision will be made whether or not to continue the observation period, and if so, the schedule to employ.

General Procedure

The PVC dust to be evaluated will be supplied by the Ethyl Corporation (Dr. Benya). A specified quantity of the dust will be administered by intratracheal instillation in a manner similar to that described by Davis, et al. (Br. J. Cancer, 31:129, 1975). A similar procedure was used by Stenback and Rowland (Scand. J. Resp. Dis., 59:130, 1978) to study talc and benzo(a)pyrene in Syrian golden hamsters.

Male rats of the Wistar strain, weighing 100 to 150 grams at the initiation of the study, are recommended. The test sample is prepared for administration by suspending it in normal saline, by sonication immediately prior to administration, so that 0.2 ml. of the suspension will contain the desired quantity of PVC dust (about 3 to 5 mg.). Each rat is anesthetized and a cannula is passed through the larynx and the 'dose' (0.2 ml. of the suspension) is given by intratracheal instillation. In order to produce maximum exposure in a minimum period of time, it is proposed that this procedure be repeated three (3) times per week for five (5) weeks for a total of fifteen (15) 'doses'. Control rats will be administered 0.2 ml. of saline in the same manner.

It is recommended that 10 rats from the PVC dust treatment group and 10 of the controls be sacrificed, autopsied and tissues taken for histopathology at the following times (from date of initiation of treatments): (a) six weeks, (b) three months, (c) four months, (d) five months, and (e) six months. The remaining rats will be held until the tissues from the six months sacrifices are examined histologically, at which time a decision will be made as to whether to continue the study or not. At autopsy, the trachea, lungs, liver, and kidneys will be removed and preserved in 10% buffered formalin for histological processing and evaluation. In addition, if suspicious lesions of other tissues or organs are observed during the autopsy, they will be removed and preserved for histological examination.

To conduct the study as envisioned in this outline, it is desired to have about 100 rats which have been treated with the 15 intratracheal instillations of the PVC dust suspensions, plus 100 saline-treated controls. In-as-much-as Ishinishi, et al. (Environ. Health Perspect., 19:191, 1977) reported a survival of 30% to 71% of the rats in their various groups after 15 weekly instillations of this type (mean of all groups was 41% survival), it is suggested that each group be initially composed of 200 rats to provide approximately 100 at the end of the 15 'dose' treatment schedule.

Comments

There are many modifications or variations of this procedure which could be employed. This particular procedure is suggested

because this methodology of administering a powder or similar material into the lung area is reasonably well established. The rather frequent treatment of rats proposed here is an attempt to demonstrate in a rather brief period, if possible, a reaction which might occur much more slowly from a more conservative treatment schedule.

A six-months study is rather short for assessing a material for its ability or tendency to produce tumors. The experimental design, however, provides the flexibility of extending the observation period, without a loss of time, should it appear desirable.

6-27-79

750
Vinyl chloride

P. F. DEISLER

Vinyl Chloride

I have just discovered this reasonably complete summary of Maltoni's studies up to 1977. The numbers are suspect, e.g., "corrected numbers" and there is little in the way of data for separate sexes. Also, the exposures are atypical in that four-hour exposures were studied for periods ranging from 17-52 weeks. A more typical exposure would have been about twice this amount. Table 13 suggests that exposure time has an effect on tumor incidence.

I have taken the results of experiment BT1 (Table 8) and plotted them on semi-log paper. If a straight line relation is obtained, then a no-effect level would be predicted at around 20 ppm. However, experiment BT15 (Table 12) gives data for lower exposures and results to 87 weeks (final results not yet located). Inspection suggests that there are effects at lower levels, possibly even 1 ppm.

Table 13, like Table 8, suggests that the dose response for angiosarcomas is not straight forward. 30,000 ppm (Table 10) really did give a good response!

Table 21 is important, since it is clear from animal stuides that VCM is a multi-site carcinogen - one obvious site to investigate would be cutaneous/subcutaneous tumors.

The Maltoni experiments could have been better designed since the doses have been chosen unevenly and are concentrated at the highest exposure levels. It seems unlikely that we could get individual animal results which would have enabled us to do some very interesting analyses of relative risk.

Don

D. E. Stevenson

DES:sas

Attachments

cc: R. E. Joyner
H. L. Kusnetz
M. B. Slomka

6/27/79

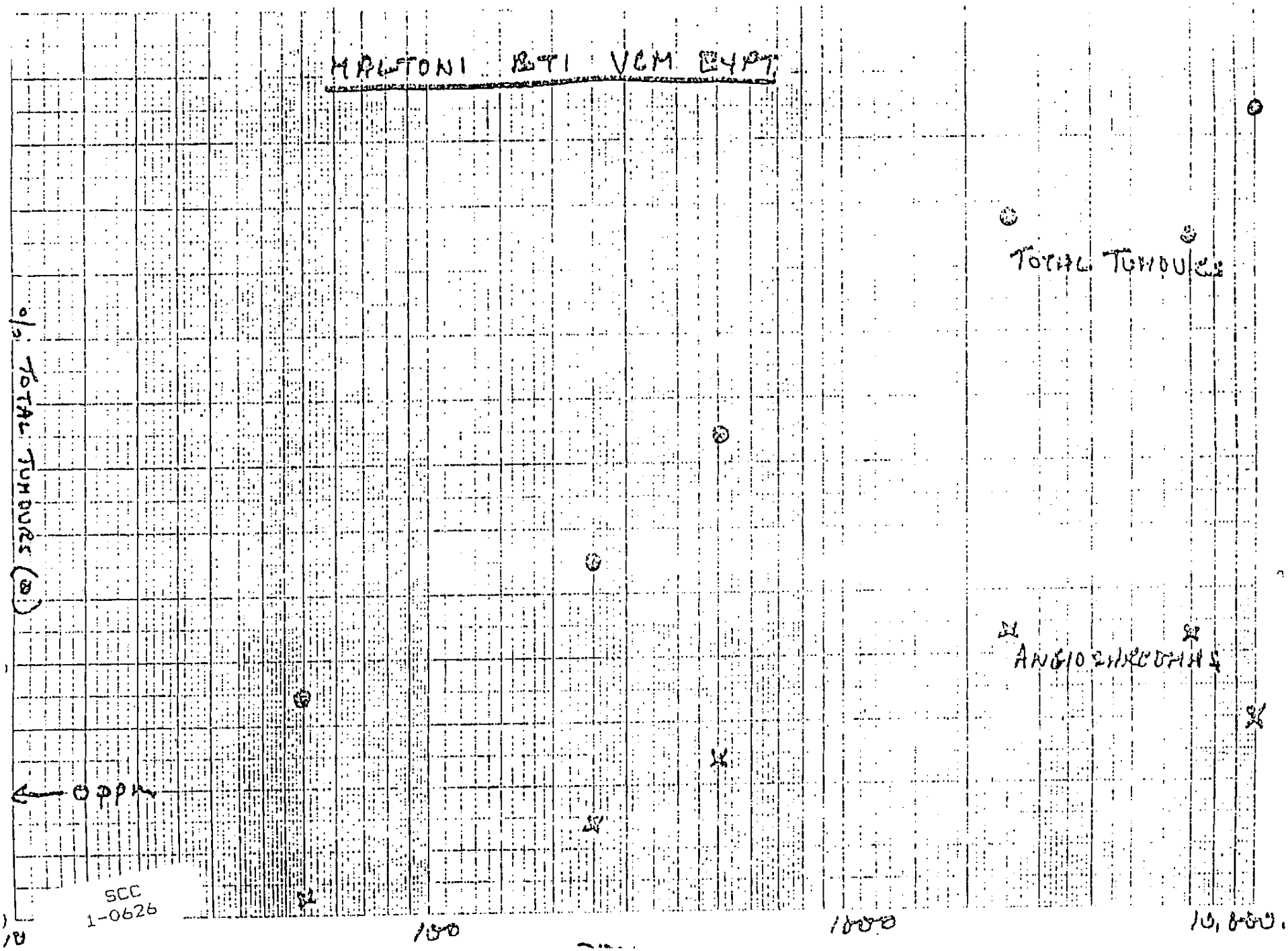
HARTONI BTI VCM EXPT
TOTAL TUMOURS
ANGIOSARCOMAS
% TOTAL TUMOURS (⊗)
0 ppm
SCC
1-0626
10
100
1000
10,000

Table 1
Plan of the Experiments on Vinyl Chloride Oncogenesis: Effects of Inhalation of Different Doses for 1 Year

		Animals: Sprague-Dawley rats				
			no.			
Exp. no.	*Treatment[a] doses VC*	*age (weeks)*	♀	♂	*total*	*per group*
BT1	10,000, 6000, 2500, 500, 250, 50 ppm; untreated controls; treated controls: VA 2500 ppm	13	265	309	577	64–96
BT2	200, 150, 100 ppm; untreated controls	13	280	265	545	120–185
BT6	30,000 ppm	17	30	30	60	60
BT9	50 ppm; untreated controls	11	200	200	400	100–300
BT15	25, 10, 5, 1 ppm; untreated controls	13	300	300	600	120

[a] The duration of treatment in each case was 4 hr daily, 5 days weekly.

Table 2
Plan of the Experiments on Vinyl Chloride Oncogenesis: Effects of Length of Exposure by Inhalation

			Animals: Sprague-Dawley rats				
	Treatment			*no.*			
Exp. no.	*doses VC*	*duration*	*age (weeks)*	♀	♂	*total*	*per group*
BT3	10,000, 6000, 2500, 500, 250, 50 ppm; untreated controls	4 hr daily, 5 days weekly, 17 weeks	21	262	288	550	60–190
BT10	10,000, 6000 ppm; untreated controls	4 hr daily, 5 days weekly, 5 weeks; 4 hr daily, 1 day weekly, 25 weeks; 1 hr daily, 4 days weekly, 25 weeks	11	420	420	840	120

Table 3
Plan of the Experiments on Vinyl Chloride Oncogenesis: Effects of Age

Exp. no.	Treatment			Animals: Sprague-Dawley rats				
	route	doses VC	duration	age	no. ♀	no. ♂	no. total	no. per group
BT5	transplacental	10,000, 6000 ppm	4 hr daily, 7 days (from 12th to 18th day of pregnancy)	19-week breeders: 12-day embryos	110	36	146	30–54
BT14	inhalation	10,000, 6000 ppm	4 hr daily, 5 days weekly, 5 weeks	1 day	45	44	89	43–46

Table 4
Plan of the Experiments on Vinyl Chloride Oncogenesis: Effects of Strain

Exp. no.	Treatment[a] doses VC	Animals: Wistar rats				
		age (weeks)	no. ♀	no. ♂	no. total	no. per group
BT7	10,000, 6000, 2500, 500, 250, 50, ppm; untreated controls	11	—	220	220	30–40
BT17	1 ppm; untreated controls	13	120	120	240	120

[a] The route in both cases was by inhalation, and the duration of treatment was 4 hr daily, 5 days weekly, 52 weeks.

Table 5
Plan of the Experiments on Vinyl Chloride Oncogenesis: Effects of Species

Exp. no.	Treatment[a] doses VC	Animals						
		species	strain	age (weeks)	no. ♀	no. ♂	no. total	no. per group
BT4	10,000, 6000, 2500, 500, 250, 50 ppm; untreated controls	mouse	Swiss	11	250	260	510	60–150
BT8	10,000, 6000, 2500, 500, 250, 50 ppm; untreated controls	hamster	Golden	11	—	268	268	32–70

[a] The route in both cases was by inhalation, and the duration of treatment was 4 hr daily, 5 days weekly, 30 weeks.

Table 6
Plan of the Experiments on Vinyl Chloride Oncogenesis: Experiments by Ingestion

Exp. no.	Treatment		Animals: Sprague-Dawley rats				
	doses VC	duration	age (weeks)	no. ♀	no. ♂	no. total	no. per group
BT11	50 mg, 16.65 mg, 3.33 mg/kg body weight in olive oil; controls: olive oil	5 times weekly, 52 weeks	13	160	160	320	80
BT27	1 mg, 0.3 mg, 0.03 mg/kg body weight in olive oil; controls: olive oil	5 times weekly, 52 weeks or more	10	300	300	600	150

Table 7
Plan of the Experiments on Vinyl Chloride Oncogenesis: Experiments by Injection

				Animals: Sprague-Dawley rats				
					no.			
Exp. no.	*Treatment*							
	route	*doses VC*	*duration*	*age (weeks)*	♀	♂	*total*	*per group*
BT12	endoperitoneal	4.25 mg in 1.0 ml olive oil; controls: 1.0 ml olive oil	4, 3, 2 times by two months and once	13	150	150	300	60
BT13	subcutaneous	4.25 mg in 1.0 ml olive oil; controls: 1.0 ml olive oil	1 injection	21	80	70	150	75

Table 8
Experiment BT1: Results after 135 Weeks (End of Experiment)

Group, treatment	Animals (S-D rats) total	Animals (S-D rats) corrected no.[a]	Animals with tumors: Zymbal gland carcinomas[b] no.	%	av. latency (weeks)	nephroblastomas[c] no.	%	av. latency (weeks)	angiosarcomas: liver[d] no.	%	av. latency (weeks)	other sites no.	subcutaneous angiomas no.	skin carcinomas no.	hepatomas no.	brain neuroblastomas no.	mammary carcinomas no.	other type and/or site[h] no.	total[i] no.
I VA 2500 ppm	96	49	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
II VC 10,000 ppm	69	61	16	26	50	5	8	59	9	15	64	3[e]	4	3	1	7	3	4[j]	38
III VC 6000 ppm	72	60	7	12	62	4	7	65	13	22	70	3[f]	3	1	1	3	—	8[m]	31
IV VC 2500 ppm	74	59	2	3	33	6	10	74	13	22	78	3[g]	3	1	2	5	1	3[n]	32
V VC 500 ppm	67	59	4	7	79	4	7	83	7	12	81	2[h]	1	1	4	—	1	3[o]	22
VI VC 250 ppm	67	59	—	—	—	6	10	80	4	7	79	2[i]	—	3	—	—	1	2[p]	16
VII VC 50 ppm	64	59	—	—	—	1	2	135	1	2	135	1[j]	1	1	—	—	2	7[q]	10
VIII No treatment	68	58	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	10[r]	6
Total	577	464	29	—	—	26	—	—	47	—	—	14	12	11	8	15	8	37	155

Exposure by inhalation to VC in air at 10,000, 6000, 2500, 500, 250, and 50 ppm, 4 hr daily, 5 days weekly, for 52 weeks.

[a] Animals alive after 26 weeks, when the first tumor (a Zymbal gland carcinoma) was observed. The percentages refer to the corrected number.

[b] Metastases to lung.

[c] Metastases to liver, lung, spleen, and brain.

[d] Metastases to lung.

[e] One intra-abdominal angiosarcoma (next to liver); 1 angiosarcoma of the lips; 1 angiosarcoma of the nose.

[f] One angiosarcoma in subcutaneous fibrosing angioma; 1 ossifying parauricular angiosarcoma; 1 intra-abdominal angiosarcoma (next to liver).

[g] One ossifying angiosarcoma of neck; 2 intra-abdominal angiosarcomas (1 next to spleen and 1 next to ovary).

[h] One angiosarcoma of uterus; 1 lung angiosarcoma.

[i] One intra-abdominal angiosarcoma (next to spleen); 1 intrathoracic ossifying angiosarcoma.

[j] One intra-abdominal diffused angiosarcoma.

[k] 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 significantly.

[l] Two Zymbal gland adenomas; 1 ovarian cystoadenocarcinoma; 1 neurilemmioma.

[m] Four Zymbal gland adenomas; 2 hepatic angiomas; 1 peritoneal angioma; 1 salivary gland adenocarcinoma.

[n] One Zymbal gland adenoma; 2 ependymomas.

[o] One pulmonary fibrosarcoma; 2 lymphomas.

[p] One Zymbal gland adenoma; 1 lymphoma.

[q] Three Zymbal gland adenomas; 1 subcutaneous angiopericitoma; 3 uterine adenocarcinomas (1 with sarcomatous component).

[r] One 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.

[s] Several animals with two or more tumors.

Table 9
Experiment BT2: Results after 143 Weeks (End of Experiment)

Group, treatment	Animals (S-D rats)	No. of animals with tumors					
		Zymbal gland carcinomas	nephroblastomas	angiosarcomas — liver	angiosarcomas — other sites	other type and/or site	total
I VC 200 ppm	120	1	3	12	1[a]	23[d]	30
II VC 150 ppm	120	2	7	5	3[b]	17[e]	29
III VC 100 ppm	120	1	10	1	—	12[f]	20
IV No treatment	185	1	—	—	1[c]	20[g]	21
Total	545	5	20	18	5	72	100

Exposure by inhalation to VC in air at 200, 150, and 100 ppm, 4 hr daily, 5 days weekly, for 52 weeks.

[a] One intra-abdominal angiosarcoma.

[b] Two subcutaneous angiosarcomas; 1 intra-abdominal angiosarcoma.

[c] One subcutaneous angiosarcoma.

[d] Five skin carcinomas; 1 subcutaneous fibroangioma; 4 mammary carcinomas; 2 liver fibroangiomas; 3 liver angiomas; 3 liver hepatomas; 1 liver colangioma; 1 intra-abdominal fibroangioma; 1 leimyosarcoma of uterus; 1 neurilemmoma; 1 orbital fibrosarcoma.

[e] Three skin carcinomas; 5 mammary carcinomas; 1 thymus angioma; 1 nasal osteosarcoma; 1 cranial osteosarcoma; 1 liver colangioma; 2 adenocarcinomas of uterus; 1 fibromixosarcoma of uterus; 1 fibrosarcoma of lung; 1 lymphoma.

[f] One skin carcinoma; 1 subcutaneous fibrosarcoma; 3 mammary carcinomas; 1 intra-abdominal angioma; 3 forestomach papillomas; 1 adenocarcinoma of uterus; 1 intra-abdominal rabdomyosarcoma; 1 kidney adenoma.

[g] One Zymbal gland adenoma; 1 skin adenocarcinoma; 1 skin sebaceous adenoma; 1 subcutaneous fibrosarcoma; 2 subcutaneous fibromixosarcomas; 1 mammary carcinoma; 1 intrathoracic rabdomyosarcoma; 3 forestomach papillomas; 1 adrenal carcinoma; 3 adenocarcinomas of uterus; 1 fibrosarcoma of uterus; 1 fibrosarcoma of scrotum; 3 lymphomas.

[h] Several animals with two or more tumors.

Table 10
Experiment BT6: Results after 63 Weeks (End of Experiment)

Group, treatment	Animals (S-D rats)		Animals with tumors							
			Zymbal gland carcinomas			nas-pharyngeal blastomas	angio-sarcomas		other types and/or site	total[d]
	total	corrected no.[a]	no.	%	latency (weeks)	no.	liver no.	other sites no.	no.	no.
I VC 30,000 ppm	60	60	31	52	43	—	17	1[b]	27[c]	51

Exposure by inhalation to VC in air at 30,000 ppm, 4 hr daily, 5 days weekly, for 52 weeks.

[a] Animals alive after 24 weeks, when the first tumor (a Zymbal gland carcinoma) was observed. The percentages refer to the corrected number.

[b] One lung angio-sarcoma.

[c] Seven Zymbal gland adenomas; 1 skin carcinoma; 1 subcutaneous fibroangioma; 2 mammary carcinomas; 1 liver angioma; 1 hepatoma; 11 forestomach papillomas; 1 ovarian angioma; 1 brain neuroblastoma; 1 Harderian gland carcinoma.

[d] Several animals with two or more tumors.

Table 11
Experiment BT9: Results after 100 Weeks

Groups, treatment	Animals (S-D rats)		No. of animals with tumors										
			Zymbal gland carcinomas	nephroblastomas	angiosarcomas		mammary tumors					other type and/or site	total[g]
	total	survivors			liver	other sites	total	histological examination	carcinomas	other malignant tumors	fibroadenomas		
I													
VC 50 ppm	300	55	6[a]	1	6	7[b]	111	90	43	2[c]	45	28[e]	128
II													
No treatment	100	28	—	1	—	—	20	8	3	2[d]	3	7[f]	24
Total	400	83	6	2	6	7	131	98	46	4	48	35	152

Exposure by inhalation to VC in air at 50 ppm, 7 hr daily, 5 days weekly, for 52 weeks.

[a] One with sarcomatous component.

[b] Two subcutaneous angiosarcomas; 1 mammary angiosarcoma; 1 heart angiosarcoma; 1 thymus angiosarcoma; 1 abdominal angiosarcoma (next to spleen); 1 ovarian angiosarcoma.

[c] Two carcinosarcomas.

[d] Two carcinosarcomas.

[e] Two skin carcinomas; 3 subcutaneous fibrosarcomas; 3 subcutaneous rabdomyosarcomas; 1 subcutaneous leiomyosarcoma; 1 subcutaneous mixed sarcoma; 1 subcutaneous fibroangioma; 1 liver angioma; 1 thymus fibroangioma; 1 mediastinal fibroangioma; 1 spleen fibroangioma; 1 uterine fibroangioma; 2 uterine adenocarcinomas; 2 hypophysis adenomas in malignant deviation; 1 Leydig cells tumor; 1 ovarian fibroma; 1 retroperitoneal liposarcoma; 1 osteosarcoma; 4 leukemias.

[f] One subcutaneous fibrosarcoma; 1 subcutaneous angiopericitosarcoma; 2 uterine fibrosarcomas; 3 leukemias.

[g] Several animals with two or more tumors.

Table 12
Experiment BT15: Results after 87 Weeks

Group, treatment	Animals (S-D rats)		No. of animals with tumors						
	total	survivors	Zymbal gland carcinomas	nephroblastomas	angiosarcomas: liver	angiosarcomas: other sites	mammary carcinomas	other type and/or site	total
I									
VC 25 ppm	120	45	3	—	3	—	10	7	20
II									
VC 10 ppm	120	51	1	—	—	—	11	5	16
III									
VC 5 ppm	120	62	—	—	—	—	13	5	17
IV									
VC 1 ppm	120	49	—	—	—	—	8	4	12
V									
No treatment	120	49	—	—	—	—	2	4	6
Total	600	256	4	—	3	—	44	25	71

Exposure by inhalation to VC in air at 25, 10, 5, and 1 ppm, 4 hr daily, 5 days weekly, for 52 weeks.

Exposure by inhalation to VC in air at 10,000, 6000, 2500, 500, 250, and 50 ppm, 4 hr daily, 5 days weekly, for 17 weeks.

[a] The number of tumors found in experiment BT1 after 135 weeks is shown in parentheses.

[b] One subcutaneous angiosarcoma.

[c] One intra-abdominal angiosarcoma.

[d] One subcutaneous angiosarcoma; 1 intra-abdominal angiosarcoma.

[e] One intra-abdominal angiosarcoma.

[f] One subcutaneous ossifying angiosarcoma; 1 orbital angiosarcoma.

[g] One ovarian angiosarcoma.

[h] Three skin carcinomas; 1 skin papilloma (nose); 1 renal adenoma; 1 lung angioma; 1 paraurieular fibrosarcoma.

[i] One Zymbal gland fibroangioma; 5 skin carcinomas; 1 subcutaneous angioma; 1 mammary carcinoma; 1 forestomach papilloma; 1 adenocarcinoma of uterus; 1 cranial osteoma.

[j] Two skin carcinomas; 1 subcutaneous angioma; 1 mammary carcinoma; 1 hepatoma; 1 adenocarcinoma of uterus.

[k] One ovarian carcinoma; 2 lymphomas.

[l] One Zymbal gland adenoma; 1 mammary carcinoma; 1 adenocarcinoma of uterus; 1 Leydig cells tumor; 1 retrobulbar fibroma.

[m] One skin papilloma (nose); 1 mammary carcinoma; 3 adenocarcinomas of uterus.

[n] One Zymbal gland adenoma; 1 skin carcinoma; 3 subcutaneous fibrosarcomas; 1 subcutaneous leiomyosarcoma; 1 mammary carcinoma; 1 ovarian gynandroblastoma; 1 fibrosarcoma of uterus; 1 salivary adenocarcinoma; 2 lymphomas.

[o] Several animals with two or more tumors.

Table 14
Experiment B15: Results after 143 Weeks (End of Experiment)

Group, treatment	Animals (S-D rats)		No. of animals with tumors					
	total	corrected no.	Zymbal gland carcinomas	hepatocellular tumors	angiosarcomas		other type and/or site	total
					liver	other sites		
I VC 10,000 ppm breeders	30	30	1	—	—	1[b]	2[c]	3[h]
II VC 6000 ppm breeders	30	30	—	—	—	—	—	—
III VC 10,000 ppm offspring	54	51	3	1	—	2[e]	2[f]	8
IV VC 6000 ppm offspring	32	32	1	—	—	2[d]	4[g]	6[h]
Total	146	143	5	1	—	5	8	17

Exposure by inhalation to VC in air at 10,000 and 6000 ppm of breeders, 4 hr daily, for 1 week (from 12th to 18th day of pregnancy).

[a] Animals alive after 22 weeks, when the first tumor (a subcutaneous angiosarcoma) arose in an offspring.

[b] One intra-abdominal angiosarcoma.

[c] One subcutaneous angiosarcoma; 1 angiosarcoma of the leg.

[d] One subcutaneous angiosarcoma; 1 intra-abdominal angiosarcoma.

[e] One liver fibroangioma; 1 liver angioma.

[f] One Zymbal gland fibrosarcoma; 1 ovarian leiomyosarcoma.

[g] One Zymbal gland adenoma; 1 skin carcinoma; 1 subcutaneous fibroangioma; 1 mammary carcinoma.

[h] One animal with two tumors.

Table 15
Incidence of Hepatic Tumors among Sprague-Dawley Rats Exposed to VC: Results after 104 Weeks

Exp. no.	Group	No. of animals: total	No. of animals: survivors	Liver tumors: angiosarcomas	Liver tumors: hepatomas	Liver tumors: total animals with liver tumors
BT10	I					
	VC 10,000 ppm	120	16	—	1	
	II					
	VC 6000 ppm	120	15	—	—	
	III					
	no treatment	249	55	—	—	
BT14	I					
	VC 10,000 ppm	46	8	10	15	19
	II					
	VC 6000 ppm	43	5	10	13	17

Exposure in air at 10,000 and 6000 ppm, 4 hr daily, 5 days weekly, for 5 weeks, at different ages: 13 weeks (BT10) and 1 day (BT14).

Table 16
Experiment BT7: Results after 136 Weeks

Group, treatment	Animals (Wistar rats)		No. of animals with tumors[a]						
	total	survivors	Zymbal gland carcinomas	nephroblastomas	angiosarcomas: liver	angiosarcomas: other sites	brain neuroblastomas	other type and/or site	total[b]
I VC 10,000 ppm	30	—	1 (10)	1 (3)	8 (4)	— (2)	1 (2)	2[c] (7)	11 (20)
II VC 6000 ppm	30	—	— (3)	3 (3)	2 (3)	1[b] (1)	1 (2)	5[f] (4)	8 (13)
III VC 2500 ppm	30	—	— (1)	— (5)	3 (6)	1[e] (2)	— (2)	2[g] (2)	4 (16)
IV VC 500 ppm	30	—	— (3)	1 (2)	4	—	—	2[h]	7 (6)
V VC 250 ppm	30	—	—	— (2)	1 (2)	1[d] (1)	—	4[i] (3)	4 (6)
VI VC 50 ppm	30	—	—	—	—	— (1)	—	1[j] (1)	1 (2)
VII No treatment	40	3	—	—	—	—	—	4[k]	4
Total	220	3	1 (17)	5 (15)	18 (15)	3 (7)	2 (6)	19 (17)	39 (63)

Exposure by inhalation to VC in air at 10,000, 6000, 2500, 500, 250, and 50 ppm, 4 hr daily, 5 days weekly, for 52 weeks.
[a] The number of tumors found in experiment BT1 after 135 weeks is shown in parentheses.
[b] One intra-abdominal angiosarcoma (next to spleen).
[c] One angiosarcoma of the interscapular fat pad.
[d] One scrotal angiosarcoma.
[e] Two Zymbal gland adenomas.
[f] Two liver angiomas; 1 hepatoma; 1 testicular mesothelioma; 1 thymus fibroangioma.
[g] One skin sebaceous adenoma (eye); 1 Leydig cells tumor.
[h] One liver fibroangioma; 1 intra-abdominal fibromixosarcoma.
[i] One skin carcinoma; 1 skin acanthoma; 1 angioma of the caecum; 1 lymphoma.
[j] One lymphoma.
[k] One pericitosarcoma; 1 Leydig cells tumor; 2 lymphomas.
[l] Several cases with two or more tumors.

Table 17
Experiment BT41: Results after 81 Weeks (End of Experiment)

Group, treatment	Animals (Swiss mice) total ♂	♀	♂ ♀	corrected number[a] ♂	♀	♂ ♀	Animals with tumors: lung tumors[b] no.	%	av. latency (weeks)	mammary carcinomas[c] no.	%	av. latency (weeks)	liver angiosarcomas no.	other vascular no.	epithelial tumors of the skin no.	other type and/or site no.	total[w] no.
I VC 10,000 ppm	30	30	60	22	28	50	35	70	36	13	47	31	8	9[d]	3[k]	2[p]	36
II VC 6000 ppm	30	30	60	26	28	54	38	70	38	8	28	33	5	9[e]	6[l]	4[q]	39
III VC 2500 ppm	30	30	60	23	30	53	30	57	43	9	30	35	11	12[f]	3[m]	2[r]	31
IV VC 500 ppm	30	30	60	29	29	58	38	66	41	7	24	37	11	18[g]	1[n]	1[s]	43
V VC 250 ppm	30	30	60	29	29	58	33	57	45	11	32	39	11	22[h]	2[o]	3[t]	40
VI VC 50 ppm	30	30	60	27	30	57	2	3.5	51	12	33	43	1	13[i]	—	1[u]	18
VII No treatment	80	70	150	74	67	141	8	6	64	—	—	—	—	1[j]	—	7[v]	13
Total	260	250	510	230	241	471	184	—	—	60	—	—	47	84	15	20	220

Exposure by inhalation to VC in air at 10,000, 6000, 2500, 500, 250, and 50 ppm, 4 hr daily, 5 days weekly, for 30 weeks.

[a] Animals alive after 16 weeks, when the first tumor (a mammary carcinoma) was observed. The percentages refer to the corrected number.

[b] Adenomas, some of which undergoing malignant transformation.

[c] In females.

[d] Three subcutaneous angiomas; 4 liver fibroangiomas; 1 heart fibroangioma; 1 ossifying interscapular angioma.

[e] One subcutaneous angiosarcoma; 2 liver fibroangiomas; 4 liver angiomas; 1 renal fibroangioma; 1 thymus angioma.

[f] Three subcutaneous angiosarcomas; 1 subcutaneous angioma; 3 liver angiomas; 2 intra-abdominal angiosarcomas; 2 renal angiosarcomas; 1 lung angioma.

[g] Two subcutaneous angiosarcomas; 1 subcutaneous fibroangioma; 1 subcutaneous angioma; 4 liver fibroangiomas; 1 liver angioma; 3 intra-abdominal angiosarcomas; 1 intra-abdominal fibroangioma; 1 renal angiosarcoma; 1 testicular fibroangioma; 1 angioma of the caecum; 1 lung fibroangioma; 1 lung angioma.

[h] One subcutaneous angioma; 6 liver fibroangiomas; 10 liver angiomas; 2 intra abdominal angiosarcomas; 1 ovarian angioma; 1 scrotal angioma; 1 lung angioma.

[i] One subcutaneous angiosarcoma; 1 subcutaneous fibroangioma; 2 subcutaneous angiomas; 2 liver fibroangiomas; 3 liver angiomas; 1 intra-abdominal angioma; 1 ovarian angioma; 1 intrathoracic fibroangioma; 1 angioma of the interscapular fat pad.

[j] One angiosarcoma of uterus.

[k] Two squamous carcinomas; 1 invasive acanthoma.

[l] Five squamous carcinomas; 1 acanthoma.

[m] One squamous carcinoma; 2 acanthomas.

[n] One acanthoma.

[o] One skin adenocarcinoma; 1 basalioma.

[p] One Zymbal gland adenoma; 1 forestomach papilloma.

[q] One subcutaneous leiomyosarcoma; 1 forestomach papilloma; 1 Harderian gland adenoma; 1 lymphoma.

[r] One forestomach papilloma; 1 parotid gland mixed tumor.

[s] One Zymbal gland adenoma.

[t] One Zymbal gland adenoma; 1 Leydig cells tumor; 1 lymphoma.

[u] One parotid gland adenocarcinoma.

[v] One subcutaneous leiomyosarcoma; 1 adenoma of colon; 1 ovarian carcinoma; 1 leiomyosarcoma of uterus; 3 lymphomas.

[w] Several cases with two or more tumors.

Table 18

Experiment BT8: Results after 109 Weeks (End of Experiment)

Group, treatment	Animals (Golden hamsters)	No. of animals with tumors						
		liver angiosarcomas	skin trichoepitheliomas and basaliomas[a]	melanomas	lymphomas	forestomach epithelial[b] tumors	other type and/or site	total[g]
I VC 10,000 ppm	35	—	6	1	—	4	2[c]	10
II VC 6000 ppm	32	1	2	2	2	7	7[d]	10
III VC 2500 ppm	33	—	1	1	1	11	3[e]	13
IV VC 500 ppm	33	2	4	—	1	7	2[f]	12
V VC 250 ppm	32	—	3	—	1	2	—	6
VI VC 50 ppm	33	—	6	1	1	4	—	10
VII No treatment	70	—	2	—	2	2	—	7
Total	268	3	24	5	8	37	14	68

Exposure by inhalation to VC in air at 10,000, 6000, 2500, 500, 250, and 50 ppm, 4 hr daily, 5 days weekly, for 30 weeks.

[a] Several cases with acanthosis and some undergoing malignant transformation.

[b] Papillomas, acanthomas, some of which undergoing malignant transformation.

[c] One subcutaneous angioma; 1 gall bladder adenocarcinoma.

[d] Two hepatomas; 2 liver fibroangiomas; 2 liver angiomas; 1 bilidcts adenocarcinoma.

[e] One hepatoma; 1 liver fibroangioma; 1 liver angioma.

[f] One subcutaneous angioma; 1 bronchial carcinoma.

[g] Several animals with two or more tumors.

Table 19
Experiment BT11: Results after 120 Weeks

Group, treatment	Animals (S-D rats) total	Animals (S-D rats) survivors	No. of animals with tumors: Zymbal gland carcinomas	nephroblastomas	angiosarcomas liver	angiosarcomas other sites	mammary carcinomas	other type and/or site	totals
VC 50.00 mg/kg I	80	2	1	2	16	2[a]	5	7[c]	29
VC 16.65 mg/kg II	80	2	2	3	9	—	6	3[d]	21
VC 3.33 mg/kg III	80	4	—	—	—	2[b]	4	3[e]	9
Control: olive oil IV	80	4	1	—	—	—	4	5[f]	9
Total	320	12	4	5	25	4	19	18	68

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.

[a] One thymus angiosarcoma; 1 intra-abdominal angiosarcoma (next to spleen).

[b] One lung angiosarcoma; 1 intra-abdominal angiosarcoma (next to kidney).

[c] One skin sebaceous carcinoma; 1 hepatoma; 1 liver angioma; 2 forestomach papillomas; 1 intestinal adenocarcinoma; 1 lymphoma.

[d] One liver angioma; 1 adrenal carcinoma; 1 lymphoma.

[e] One subcutaneous sarcoma with angioblastic component; 1 intra-abdominal ossifying sarcoma with angioblastic component; 1 bladder papilloma.

[f] One skin carcinoma; 1 papilloma of the auditory duct; 1 bladder carcinoma; 1 adrenal carcinoma; 1 reticulosarcoma.

[g] Several animals with two tumors.

Table 20
Experiment BT27: Results after 57 Weeks

Group no.	Treatment: dose	Treatment: length (weeks)	Treatment: ongoing	Animals: no. at start ♂	Animals: no. at start ♀	Animals: no. at start total	Animals: survivors ♂	Animals: survivors ♀	Animals: survivors total	Animals: present age (weeks)	Tumors: mammary tumors: histologically examined total	Tumors: mammary tumors: histologically examined fibroadenomas	Tumors: mammary tumors: histologically examined carcinomas	Tumors: others
I	1 mg	57	+	81	77	158	48	67	115	67	11	—	—	1 subcutaneous fibrosarcoma
II	0.3 mg	57	+	82	77	159	51	48	99	67	6	—	—	1 renal pelvis carcinoma
III	0.03 mg	57	+	78	85	163	48	58	106	67	14	1	2	1 malignant histiocitosis
IV	controls: olive oil	57	+	82	77	159	38	57	95	67	6	—	—	1 forestomach papilloma; 1 stomach adenomatous polypus; 2 lymphomas
Total				323	316	639	185	230	415		37	1	2	7

Exposure by ingestion (stomach tube) to VC in olive oil at 1, 0.3, and 0.03 mg/kg body weight, once daily, 4–5 days weekly, for 104 weeks.
[a] Sprague-Dawley rats, 10 weeks old at start.

Table 21
Tumors Presently Correlated to VC Exposure (by Inhalation) on Experimental Rodents and Man

Species	*Angio-sarcomas of liver*	*Tumors of brain*	*Tumors of lung*	*Lymphomas and leukemias*	*Hepatomas*	*Angio-sarcomas*	*Nephroblastomas*	*Sebaceous cutaneous carcinomas*	*Other cutaneous epithelial tumors*	*Mammary carcinomas*	*Forestomach papillomas and acanthomas*
Rat	+	+			+	+	+	+	+	(+)	+
Mouse	+		+			+		+	+	+	(+)
Hamster	+		(+)	+		(+)			+		+
Man	+	(+)	(+)	(+)	(+)						

Table 22
Reported Cases of Angiosarcoma of the Liver among Workers Exposed to Vinyl Chloride

Country	Polymerization	Other occupation	Total
Belgium	1	—	1
Canada	10	—	10
Czechoslovakia	2	—	2
Federal Republic of Germany	8	1	9
France	5	—	5
Great Britain	2	1	3
Italy	2	1	3
Japan	1	—	1
Norway	1	—	1
Rumania	1	—	1
Sweden	2	1	3
Switzerland	1	—	1
U.S.A.	19	2	21
Yugoslavia	2	—	2
Total	57	6	63